Henry Ford Hospital Medical Bulletin

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1957

THE REFLECTION OF A SURGEON IN THE PROGRESS OF HIS ART*

GROVER C. PENBERTHY, M.D.**

The gracious invitation to present the Roy Donaldson McClure Lecture I consider a very particular honor, but my acceptance was with a feeling of humility. The previous speakers on this occasion to honor the memory and professional contributions of Dr. McClure were men who made singularly outstanding contributions to the surgical field as well as close personal friends of long standing. Tonight the essayist speaks from the latter point of view — with a long association and a deep admiration and affection for him. I know I am joined in these feelings by his many local friends and associates.

Dr. McClure not only lived in a period of great progress in surgery, but was a vital part of it. He did not simply watch the parade of progress, but marched at the head of it. He came by his spirit of leadership and interest in medicine naturally; his father, grandfather and great-grandfather having been doctors before him; a rich heritage. In medical school at Johns Hopkins, he came under the influence of the big four — Osler, Welch, Halsted and Kelly. Later on he studied under Alexis Carrel[1] at the Rockefeller Institute. With all of this background of the best in medical forebears plus a splendid galaxy of teachers, Dr. McClure was a modest person, kindly and always willing to help, which brought forth the best efforts and cooperation of his students, house officers and associates. A naturally reserved and dignified person, he appeared to some unapproachable, but his dedication to the best in medicine, his loyalty and kindness, was obvious to those who knew him at all well.

Let us picture the state of surgery when Dr. McClure began his professional career. Certain areas of the body were forbidden to the surgeon. The peritoneal cavity had been frequently entered and laparotomy was a common operation. The chest, cardiovascular system, the cerebrospinal tract and the pancreas were not considered possible of surgical approach. The common method of introducing fluids was by proctoclysis or hypodermoclysis. Blood transfusions were rare. The development of modern methods of fluid and electrolyte replacement was not well considered until the 1920's even though Andries and McLean,[2] and Hartwell and Hoguet[3] in 1912 showed that animals with obstruction lived longer when intravenous salt solution was given. Credit for the modern concepts of fluid balance must go to Dr. Coller and his associates.[4]

It was in 1924 that Davidson[5] under Dr. McClure's stimulus developed the tannic acid method of treating burns. This was a decided step forward, for even if it is not now a commonly accepted treatment, it not only focused attention on the care of the burned patient, but indicated the importance of fluid replacement of the burned patient. Along with other fluids, transfusions of blood were administered to these patients, and this stemmed from one of Dr. McClure's early interests, the transfusion of whole blood. With Eugene Pool in 1910,[6] while a house officer at the New York Hospital, he developed a method for transfusion by direct suture of the donor's vessel to the recipients. This was the first type of transfusion I saw when an intern at the City Hospital in New York. Dr. McClure[7] reported 150 transfusions in 1917, and

*The Roy D. McClure Lecture presented April 16, 1957.

**Detroit, Michigan.

recommended transfusion for the treatment of shock. Transfusions today are routine, perhaps almost too much so, but it is almost unthinkable that one could do extensive surgery without the transfusion of blood.

Despite the clear cut studies carried out by Dr. McClure and his associates in Baltimore and in New York which indicated the possibilities of extensive blood vessel surgery, the development of this field was long delayed. Many factors were responsible for this; safety factors for the patient were not so well developed, particularly in the direction of anticoagulants, now used routinely. Infection was more difficult to control so that a great deal of the surgeon's work was taken up by handling of these problems, many of which were time consuming and arduous. Adequate control of fluid and electrolyte balance was not sufficiently considered. Blood was not readily at hand, and the dangers of transfusion were greater. Transfusion then was no simple matter and was performed first by suture of the donor's vein to that of the recipient. Later this was simplified by the use of syringes to draw the blood from the donor and to inject it into the recipient. This was a major procedure and preformed in the operating room. Anyone who has not seen this performance would hardly believe that it served the same purpose that the present day transfusion fills. Whole blood without anticoagulant was used. When anticoagulants, chiefly sodium citrate, were utilized this permitted less rapid infusion of blood and a series of procedures were developed. Instead of the use of multiple syringes, such were developed which allowed withdrawal of blood and its injection with the same syringe and reduced the number of necessary personnel. Many modifications of such instruments were developed. Vacuum tubes were used and also complicated closed systems for drawing and giving of blood were designed. Blood was always freshly used. Banking of blood is a relatively late development and Dr. McClure interested himself in this problem, carrying out extensive studies with Dr. Hartman on the preservation of blood.

The difficulties in the field of blood transfusion and in vivo anticoagulation alone were enough to retard vascular, and especially cardiac surgery. In addition, the many other problems which present themselves to a busy surgeon such as Dr. McClure, kept him engaged in doing the obvious, necessary and more readily feasible operations.

The surgery of the thyroid gland took tremendous steps forward in Dr. McClure's time and he contributed greatly to this advance. The removal of the thyroid, especially in Grave's disease, the then prevalent type, was attended by a high mortality; minimal thyroidectomies were the rule, attended by a high recurrence rate. Dr. McClure recognized the effect of iodine on this disease and was for many years active in developing the use of iodized salt in the prevention of simple goiter. Today, with the use of iodine and the antithyroid drugs, thyroidectomy is ordinarily not a serious problem.

Since Dr. McClure was a resident under Halsted it was only natural that he should be interested in carcinoma of the breast. Careful dissection, exact hemostasis and wide removal of the breast, pectoral muscles and lymph nodes of the axilla, with careful handling of the tissue, was not only practiced by Dr. McClure, but he also played an important role in disseminating the principles of Dr. Halsted by his teaching and writings. Variations on this theme have been presented, such as more extensive removal of the lymph nodes in the mediastinum and neck and combinations of x-ray and surgery, but their net added effectiveness is still open to question. The procedure of choice and with the best results still seems to be that which Dr. McClure practiced.

Dr. McClure was commanding officer of the 33rd Evacuation Hospital during World War I and went to France with this Unit. It was at this time that an infection of the pleural cavity was a common reason for operation. In certain forms a 70% mortality of cases operated upon was reported in the Medical History of World War I;[8] at Camp Dodge where I was stationed late in 1917, it was about 75%. It was Dr. McClure's close friend, Dr. Evarts Graham, the 1956 guest speaker, and recently deceased, who, as a member of the Empyema Commission,[8] helped to establish the principles of care for patients with empyema, which eventually lowered the mortality to less than 4%. The operation for this condition was a common one in Dr. McClure's early days. In the period 1926-36, Dr. Benson[9] and I collected the cases from Children's Hospital and reported 5,868 patients classified as having had pneumonia, and of this number, 407 or 7%) developed empyema which required surgical drainage. Today in the same hospital approximately 6 cases are reported each year. In 1941, after the advent of chemotherapy, 144 patients[10] were reported with a mortality of 2.1%. There are many young surgeons in training today who have never seen a case of empyema. This has resulted from the use of sulfa drugs and antibiotics in early control of primary lung infection, such as lobar and bronchopneumonia. While the use of antibiotics has drastically lowered the incidence of empyema, those cases that we do see on the rare occasion are somtimes more troublesome because of the changes in bacterial flora involved, due to previous antibiotics used, and partly because of the tendency for these cases to be treated medically longer and referred to the surgeon later than formerly, and often after the patient has become debilitated.

In these same early years of Dr. McClure's surgical experience, hematogenous osteomyelitis was a common condition requiring surgery. In 1928 and 1929 it is noted that 101 operations were performed at either the Children's Hospital or one of the associated institutions, and there were frequent crippling recurrences. In the past several years few operations have been performed for this condition.

For years we conducted a convalescent hospital at Farmington, which was largely populated with these and other cases resulting from infections. Today Farmington is closed, the case load not warranting its continuance. Many of these previously common infections are rarely, if ever seen today.

Wound infections are rarer and when seen are much easier of control. You all know the reason for this. It is due to the use of sulpha drugs and antibiotics. Dr. McClure, as a member of the Surgical Section of the National Research Council during World War II, occupied a place of leadership in the application of these aids in the control of infections. One of his students, Dr. William Altemeier, now Professor of Surgery at Cincinnati, has contributed extensively to our knowledge of the use of antibiotics and the sulpha drugs and is an outstanding authority in this area. This was not his only important contribution during World War II, he having served on the Amputee Committee, which stimulated the development of our modern and effective prosthetic devices.

Reference has already been made to Dr. McClure's studies with Carrel. Methods of end-to-end suture, and the transplantation of organs, indicated not only the possibilities of vascular surgery but laid the foundations for the advances in this area which have initiated a whole series of operations now performed, which fifteen years ago were not thought to be possible. Recently at the Central Surgical Association meeting

Dr. Szilagyi,[11] who served his apprenticeship under Dr. McClure, reported 264 cases of replacement of arteries by homografts. Dr. Blalock's development of the operation for correction of the Tetrology of Fallot utilized these same principles.

Intestinal obstruction in the days of the young surgeon McClure was a highly lethal problem, the mortality being somewhat in the neighborhood of 50%. When a case of obstruction was presented in the early 20's, there was but one edict — operate and operate fast. The longer the delay, the less chance the patient had for survival; or at least this was the concept. In 1924 Robertson Ward[12] developed a method for suction drainage of the stomach, and a few years later Owen Wangensteen[13] began his studies on duodenal drainage, negating as these procedures did, the need for immediate surgery. This was a courageous undertaking and one of the outstanding surgical contributions for the period. Great criticism was raised against the concept that by the use of suction drainage patients with obstruction might be saved. It is significant that when Wangensteen made his clinical studies on obstruction, animal experimentation did not play an important role. After the demonstration that control of distention seemed the key to the problems of obstruction, Taylor, Weld and Harrison,[14] Herrin and Meek,[15] and Burget, Martzloff, Thornton and Suckow[16] showed that if distention in animals was controlled, the animals lived. It was further demonstrated that even without obstruction, if the gut was distended, animals died with signs of obstruction. This was a clear eut demonstration of corroboration of clinically developed concepts by animal experimentation. This indicated quite clearly the sequence of events in intestinal obstruction and gave evidence that, without distention, the sequelae of simple obstruction did not occur. Extension of the therapeutic effects of the control of distention was further presented here in Detroit at the Receiving Hospital by our own Dr. Charles Johnston,[17] with the development of intestinal intubation. Now in the presence of obstruction we recognize the necessity for decompression in preparation of the patient for operation.

Dr. McClure recognized and supported the cause of animal experimentation as it applies to clinical disease and fundamental biological principles. When the future of animal experimentation was threatened in this area, he mobilized support to refute the claims of the antivivisectionists. Dr. Johnston, who acted as secretary for the group, supporting the cause of progress in medicine, tells me that Dr. McClure in his finest effective way brought tremendous support not only by his own appearance, but by mobilization of support which only he could have arranged. As an outgrowth of this action Michigan has a statute which recognizes animal experimentation as reasonable and necessary to medical and veterinary progress.

Dr. McClure occupied a position of vantage to view the development of surgery of the nervous system. Dr. Harvey Cushing who had preceded him several years as a resident under Dr. Halsted had already begun to make contributions in this field. Tic douloureux was a most uncomfortable problem for a patient and a hopeless one for the doctor. In 1909, Drs. Spiller and Frazier[18] described a surgical approach for the section of the sensory root of the ganglion of the fifth nerve, which with some modifications is a standard procedure used today. A contemporary of Dr. McClure's at Hopkins, Dr. Walter Dandy[19] published studies on methods of visualization of the

ventricle of the brain in 1918. This opened great possibilities for more accurate diagnosis of intracerebral lesions. Brain abscess was a particularly lethal condition for which there was no adequate treatment.[20] Close friends and associates of Dr. McClure's, Drs. Frazier, Kahn, Dandy, Coleman, Horrax and King, all made contributions to this serious condition. Today, with the advent of better methods for control and prevention of infection, brain abscess is relatively rare. Neurosurgical operations today are common and extensive. I would be remiss if in the mention of the development of neurosurgical procedures I did not mention the role of a specialist which we see seldom today — the neurologist. Dr. William Spiller was one of these, who, while not a surgeon, played a great role in the specialty of neurosurgery. I have already mentioned his role in the treatment of tic douloureux. He directed Dr. Edward Martin,[21] an associate in the Department of Surgery at the University of Pennsylvania in 1911, in the performance of the first cordotomy for the relief of pain of organic origin. This procedure is a standard one for severe unrelenting pain today. It is interesting to quote Dr. Martin as follows: "The surgical task assigned to me by Professor Spiller is to make a transverse incision into the spinal cord roughly 2 mm. in length of similar depth and with its posterior end 3 mm. anterior to the entrance of the posterior root, this cut to be bilateral." Today the neurosurgeon is largely his own neurologist, neurology and psychiatry being more closely related.

Dr. McClure also had a sustaining interest in the early ambulation of the post-operative patient, which interest is reported to have dated back when he was a house officer under Eugene Pool in New York, with encouragement given the patient who was bed-fast to move his lower extremities and the advocation of early rising. Supplementing this early physical exercise and in contrast, he witnessed a complete change in the concept of ambulation, for in his period with Dr. Halsted the postoperative hernia patient was kept inactive in a body plaster cast to permit the wound to heal.

Another field of surgery in which Dr. McClure was interested is that which pertains to the newborn and infant, as shown by his association with Dr. Edward Park[22] in their studies pertaining to the thymus gland in 1913. Pediatric surgery, like cardio-vascular surgery, neurosurgery and thoracic surgery, has made outstanding progress — a major part due to earlier diagnosis, to the better understanding of the preoperative preparation, the interpretation of X-ray films, and anesthesia; this latter due to the medical anesthesiologist's knowledge of the physiology of the respiratory, cardiovascular and cerebral systems. In Dr. McClure's early period in surgery the drop ether method was in vogue, with intratracheal and nitrous oxide-oxygen anesthesia rapidly being explored and developed.

A monument which will stand out as a memorial to our beloved colleague is the Central Surgical Association, founded in 1940, largely through his interest and enthusiastic perseverance in gaining the help and support of some members of the American Surgical Association and others. The part he played is indicated in the following rather lengthy quote taken from the Presidential Address delivered at Rochester, Minnesota, February, 1956, by Dr. Rudolf J. Noer,[23] formerly with Dr. Johnston at the Wayne State University Medical School, and now Professor of Surgery at the University of Louisville. "In our section of the United States the more promising younger surgeons do not have the opportunity for self-expression and stimulation of friendly

and intimate contacts with each other that are open to men of similar abilities and aspirations in other parts of the country. There is real place and purpose for a central (states) surgical association. I know of a dozen eligible, grade A, high-class, young surgeons in Detroit and Michigan who would be excellent material . . . and I have good reason to believe that other cities in the central states have similar groups of eligible men . . . Dr. Roy McClure, speaking on 'The Inauguration of the Central Surgical Association' said, 'My election to this office is probably a token of recognition of a role played in the formation of our society, and while it is true that the concept of the organization originated with me . . . the greater credit of its sound foundation belongs to those Fellows of the American Surgical Association who have agreed to act as its sponsors . . . Some years ago I came to realize that a great many able, well-established, and excellently qualified surgeons had been barred from inclusion in the senior surgical societies, mainly because of the "closed number" policy, while the oncoming generation of young men who have an increasingly better foundation training had even less chance . . . I could not help reflecting on the curious circumstance that of all the important cartographic divisions of our country, the potentially most important one, the Mid-West, was the only one lacking its own surgical society. These considerations made it clear that an unmistakable need existed for a surgical society with its headquarters in the Central and Great Lakes region . . . This society has been projected as a proving ground for young surgeons . . . a stimulus when this is most needed; as a bridge between the time of completion of residency, acceptance by the Boards, and arrival at the period or recognition as surgeons — a time interval during which many young surgeons stagnate through inaction and lack of stimulation by a scientific surgical society . . . I was interested to note that times and people change but little, for those who demurred offered the same objections as those advanced by the opponents of Samuel Gross and the other founders of the American Surgical Association, in 1879. The claim was made then, as now, that with the country full of all sorts of surgical societies there was no need for such an organization'." The Central Surgical Association today is considered an outstanding regional society, with a steadily increasing attendance by members and guests at the annual meetings.

In relating the influence and the part played by Dr. McClure in the progress of surgery since the turn of the century, mention should be made of his interest and contribution in providing opportunities for the training of young men ambitious to gain position in the field of surgery. The following personally known to me, have made names for themselves: the late Edward Davidson and the late Sidney Allen, Francis Chunn, Brian Blades, Henry Harkins, Edward Compere, Samuel Marshall, Conrad Lam, William E. Johnston, D. Emerick Szilagyi, William Altemeier, Laurence Fallis and Brock Brush. I realize that there are many other young men who have benefitted by Dr. McClure's guidance and have made names for themselves, but as mentioned, the above surgeons I knew and have followed their progress with interest.

Far from the least of Roy McClure's manifold accomplishments, in addition to the training and stimulation of the doctors to whom I have just referred, was the development of the organization and philosophies, along with Drs. Sladen, Hartman, Smith, Pratt, Doub, Mateer and others, of this splendid institution in which we are gathered this evening, and which will long perpetuate his memory and his endeavors.

I have related only a few of the changes which have occurred in surgery during Dr. McClure's professional life. The young surgeon of today does not have many of the problems which he daily faced. So many problems were settled that one might assume that the opportunity to make fundamental contributions to surgery is less today. On the contrary, the advances which have been made and with which Roy McClure was concerned, have opened new possibilities for progress.

While he was ever concerned with the best in surgery, I prefer to remember him for his steadfast friendliness. Never one to make friends quickly; no flamboyant spirit his, he held them with his quiet genuine interest, his kind frankness and dependability. Quick with appreciation, but slow to ire; he tolerated no meanness. He counted among his friends men of all stations. I considered myself fortunate to be counted as one of these, and to have been asked to speak tonight, not because of or about any contribution I have made, as former speakers on this occasion, but rather as a humble friend who admired him for himself and enjoyed his confidence and warm friendship.

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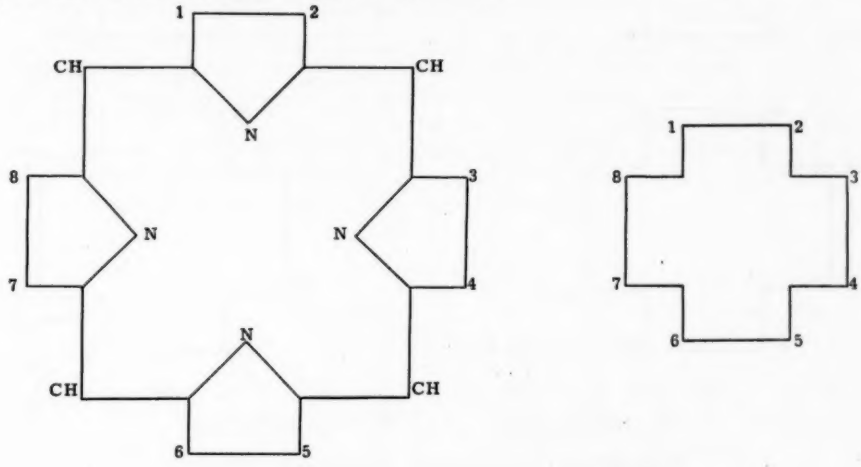
PORPHYRIA — AN "ENZYME LESION"
REVIEW OF BASIC AND CLINICAL ASPECTS

W. J. TREANOR, M.D. — C. E. RUPE, M.D.*

As knowledge of cellular bio-chemistry increases, physicians have more and more begun to think of disease processes in terms of defects or alterations in the myriad of chemical reactions within the cell. We hear now in discussions of diseases such as Cushing's disease, pernicious anemia, gout and adrenogenital syndrome, the term "enzyme lesion" or enzymatic defects. The term "enzyme lesion" was coined by Gerti Cori who described the first one completely understood — glycogen storage disease. An intimate knowledge of bio-chemistry is becoming as valuable a tool in clinical medicine as the stethoscope or palpating hand. The disease here presented, acute intermittent porphyria, affords an opportunity to review the important metabolism of a group of chemical compounds known as the porphyrins. The porphyrins are much more important than porphyria. Porphyria is very uncommon, whereas the porphyrins are important in the cellular activity of all the cells of the body.

The porphyrins comprise a large class of pigments, and the exact chemical constitution of the majority of them is unknown. Porphyrins are found throughout the animal and vegetable kingdom. Chlorophyll, for example, intimately involved in photo-synthesis, is a porphyrin containing magnesium. All the porphyrins contain the porphin nucleus as their basic structure. Porphin may be synthesized, but it is purely a laboratory creation and does not exist in nature. It is composed of four pyrrole rings connected by four methene bridges. By the addition of side chains on carbon atoms 1 through 8, all the porphyrins may be represented.



PORPHIN

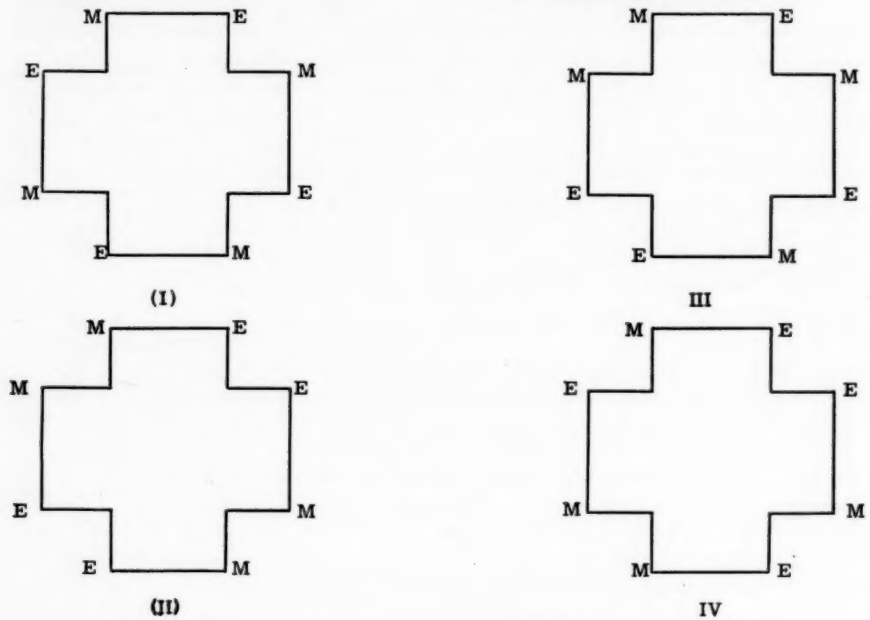
PORPHIN (SHORTHAND REPRESENTATION)

FIGURE I — BASIC COMPOUND PORPHIN

*Department of Medicine, Medical Clinic No. 4.

In figureI I the basic compound porphin is represented. To simplify its representation the shorthand method of Fischer is usually used as shown. The porphyrins which demand our interest in clinical medicine, and whose structure will be shown, are protoporphyrin, coproporphyrin and uroporphyrin.[1] These compounds are important only because they are intermediates in the production of the metalloporphyrins — hemoglobin, oxidases, catalases, peroxidases and cytochromes, all of which are respiratory enzymes. It should be emphasized that uroporphyrin, coproporphyrin and protoporphyrin are steps in the synthesis of the metalloporphyrins and are not breakdown products.

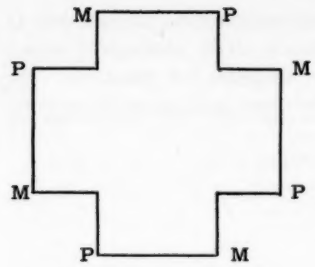
The question arises regarding the numbering of the porphyrins. For example, we read of uroporphyrin I and uroporphyrin III. The numbering has its origin in the classic work of Hans Fischer, who in 1937 synthesized a basic porphyrin compound which he called etioporphyrin, a tetramethyltetraethyl porphyrin, (again only a synthetic compound). This is represented in figure II using the shorthand symbol of Fischer for the porphyrin nucleus and showing the four possible isomers. Any porphyrin having just 2 different side chains and 4 of each has only 4 possible isomers.



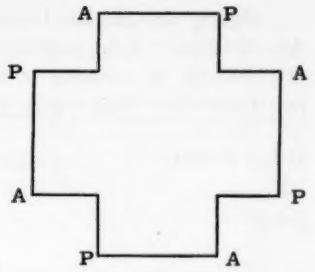
M Methyl (CH_3) E Ethyl (CH_3CH_2)

FIGURE II — ISOMERIC ETIOPORPHYRINS

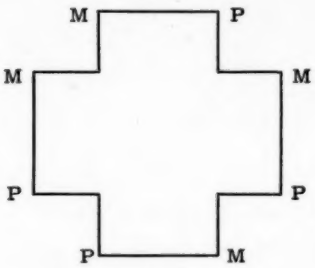
Regarding the structure of the clinically important porphyrins, coproporphyrin has side chains of methyl and propionic acid, and uroporphyrin has acetic acid and propionic acid for side chains. Again 4 isomers of each are possible, but only numbers I and III exist naturally, and these are shown in figure III.



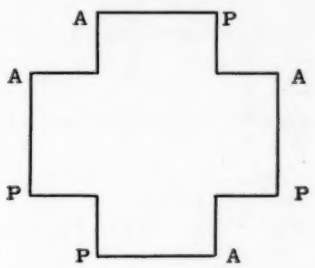
Coproporphyrin I



Uroporphyrin I



Coproporphyrin III

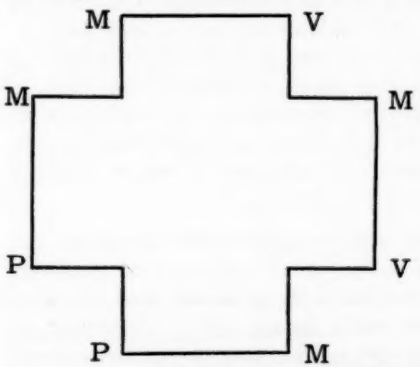


Uroporphyrin III

M Methyl (CH_3) P Propionic Acid (CH_2CH_2COOH) A Acetic acid (CH_2COOH)

FIGURE III — PROTOPORPHYRIN WITH SIDE CHAINS

Proto porphyrin is slightly different in that it has 3 side chains, methyl, vinyl and propionic acid and 15 isomers. The protoporphyrin found naturally is type 9 and is represented in figure IV. It is so called simply because it was 9th in the series listed by Fischer. Here the parenthetical type III might lead to some confusion. However, this refers only to the fact that protoporphyrin type 9 is related to type III of the etioporphyrins since all the methyl groups are in the same position, and this type III designation is usually added to show this relationship.



M Methyl (CH_3)

V Vinyl ($CH\ CH_2$)

P Propionic Acid (CH_2CH_2COOH)

FIGURE IV — PROTOPORPHYRIN NO. 9 (Type III)

Having now discussed individual porphyrins, we will now review the synthesis to determine just where porphobilinogen fits into the picture, since, although it is not a porphyrin, its presence in the urine establishes the diagnosis of porphyria. The porphyrins have their origin from succinic acid of the citric acid cycle. (figure 5).

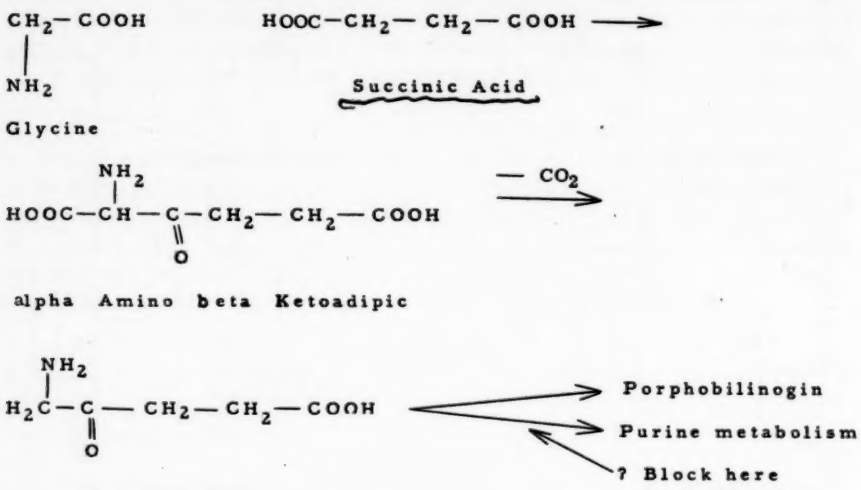


FIGURE V — SYNTHESIS OF DELTA-AMINOLEVULINIC ACID

To succinic acid is added glycine from the glycine pool and alpha-amino-beta-ketoadipic acid is formed. This is decaraboxylated to delta-aminolevulinic acid and two molecules of delta-aminolevulinic acid fuse to form porphobilinogen. (figure 6).

Delta-aminolevulinic acid is not simply a stage in the path from the citric acid cycle to the porphyrins, but is rather a fork in the metabolic road since it is also deaminated to form ketogluteraldehyde and progresses into the purine metabolism. It is here that an enzymatic block might occur in the conversion of delta-aminolevulinic acid into the purines with the result that more delta-aminolevulinic acid could be forced into porphyrin synthesis at the expense of the purines.[3] Manifestations of porphyria might, therefore, be due to diminished purine metabolism rather than an overabundance of presumably "toxic" porphyrin intermediates. To come back to porphobilinogen, the metabolic pathway to this point is well established. However, the exact pathway beyond is speculative; presumably on a gross scale it may be presented as shown in figure VI and VII.

In this process the uroporphyrin I and coproporphyrin I are formed as side products and excreted. As far as the excretion of these compounds is concerned, corproporphyrins are excreted in detectable amounts in the urine and stool of normal individuals. The normal values of corproporphyrin in urine is 100 - 300 micrograms; 60 to 90% of this is in the form of isomer type I. Uroporphyrins are not excreted in detectable amounts in normal persons, although uroporphyrin may be shown in

FIGURE VI
SYNTHESIS
OF
PORPHOBILINOGEN

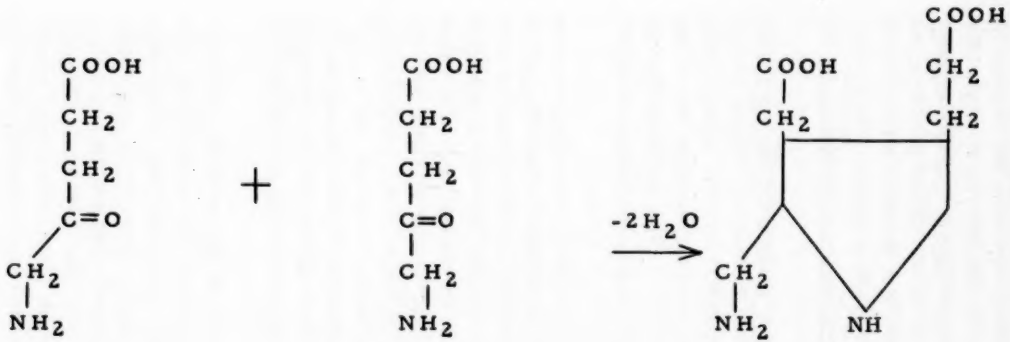
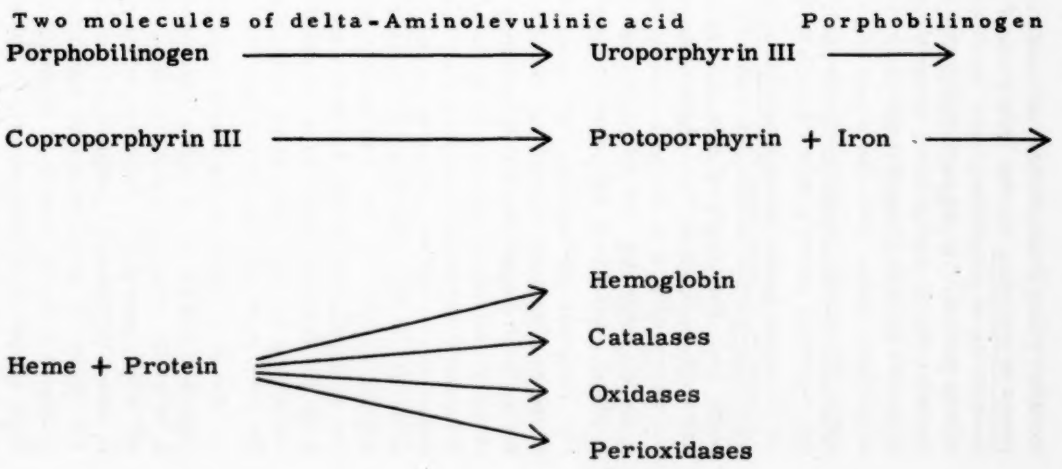


FIGURE VII
METABOLIC
PATHWAYS
BEYOND
PORPHOBILINOGIN
(Schematic)



the urine by more precise methods not readily available. Porphobilinogen is not normally present in the urine. This has great practical significance then since the diagnosis of porphyria for all practical purposes is made by finding the uroporphyrin or porphobilinogen in the urine. The Schwartz-Watson Test for porphobilinogen[4] is readily available, and this is usually positive during the acute stages of acute intermittent porphyria, and in some of the cases of mixed porphyria. It is not positive in porphyria erythropoietica or porphyria cutanea tarda, but it may be positive in latent porphyria. Coproporphyrinuria has in itself no diagnostic value since its presence may be symptomatic and indicate another disease process. This will be discussed later.

Clinically, porphyria may be defined simply as an INBORN ERROR in porphyrin metabolism. Various classifications have been presented but that of Watson is most widely used. Porphyria is divided into two main groups: Porphyria erythropoietica and porphyria hepatica. This classification is based upon the apparent site of the abnormal porphyrins in the bone marrow and in the liver. The porphyria hepatica is further subdivided into 4 groups, late porphyria, acute intermittent porphyria, porphyria cutanea tarda and mixed porphyria.

Porphyria erythropoietica (also called congenital porphyria, although in a sense all the porphyrias are congenital or inborn errors of metabolism) is the rarest of all the forms of porphyria and is characterized by splenomegaly and appearance early in life of sensitivity to light with the formation of skin lesions. This type of porphyria is apparently not familial, and there is no difference in the sex incidence. Red stained diapers may be the first clue to its presence, but usually vesicles or bullae with sun sensitivity are the trade mark of porphyria erythropoietica. These bullae become infected, necrotic and show deep scarring, producing severe mutilation, and at times loss of fingers, toes or ears has been noted. Hypertrichosis is often present in this form. The abnormal prophyrins are produced in the bone marrow and the developing erythrocytes may show fluorescence. Uroporphyrin I and coproporphyrin I are found in the urine; porphobilinogen is not excreted.

Porphyria hepatica is the second major classification of the porphyrias. Porphyria hepatica is familial and is slightly more common in women. The usual age of onset is 20 to 40. *Acute intermittent porphyria* is the first type under this classification, and it may present with abdominal, neurologic or psychic symptoms in combination or alone. The abdominal complaints may mimic any sort of acute abdominal condition. The ability of the porphyrin to masquerade as an acute abdominal emergency is attested to by the number of abdominal scars which these patients may present. Index of suspicion of porphyria is to be multiplied for each scar in a patient presenting with acute abdominal pain. (The pain is usually cramping in nature and, by way of help in differentiation, although leucocytosis is usual, the abdomen is usually soft and tenderness is minimal). Involvement of the nervous system may occur in any of its parts — central, peripheral or autonomic and consequently may take many forms. The paralysis is of the flaccid variety and may vary from foot or wrist drop to a flaccid quadriplegia. Paralysis may progress in a manner suggesting Landry's paralysis. The Guillain-Barre syndrome may be mimicked. Cerebral spinal fluid is usually normal except for minimal protein elevation. The cranial nerves may be attacked with facial weakness or ocular paralysis. Pain in the legs to suggest diabetic neuropathy may occur

before or with the paralysis. The degree of pain will vary with the degree of peripheral neuritis. Despite the presence of paresthesias, sensory changes are generally absent. Coma, convulsions and epileptiform attacks may occur. The mental changes possibly embrace the field of psychiatry. As a matter of fact, Waldenstrom discovered most of his cases of porphyria by simply testing the urines of a large number of patients in Swedish mental hospitals. Before the acute attack comes on, the patient may have had a long history of psychoneurosis.

Porphyria cutanea tarda resembles the porphyria erythropoietica because of the skin lesions and photosensitivity. However, the age of onset is from 40 to 60 years and the skin lesions, though similar, are less mutilating and hepatic dysfunction is often present. If the cutaneous lesions are present in addition to neurologic or abdominal manifestations, then these cases are referred to as *mixed porphyria;* and if the patient appears to be well but yet excretes porphobilinogen or uroporphyrin in the urine, the patient is said to have *latent porphyria.*

An important point must now be raised regarding porphyrinuria as opposed to porphyria. It should be emphasized that the finding of an excessive amount of coproporphyrin in the urine does not make the diagnosis of porphyria by itself. This merely represents porphyrinuria or, to be more specific, coproporphyrinuria and is merely a manifestation of another disease process. Coproporphyrinuria has been found in a large variety of diseases such as infectious hepatitis, obstructive jaundice, pernicious anema, hemolytic anemia, poliomyelitis, Hodgkin's disease, Laennec's cirrhosis and in

		PORPHOBILINOGEN	UROPORPHYRINS	COPROPORPHYRINS
NORMAL		NEGATIVE	NEGATIVE	Total 100-300 MCG Type I (60-80%) and Type III
PORPHYRIA ERYTHROPOIETICA		NEGATIVE	Type I	Type I
PORPHYRIA HEPATICA	ACUTE INTERMITTENT	POSITIVE	Type I	Type III
	PORPHYRIA CUTANEA TARDA	NEGATIVE	Type I	Type III
	"MIXED" PORPHYRIA	MAY BE POSITIVE	Type I	Type III
	"LATENT" PORPHYRIA	INTERMITTENTLY POSITIVE	Type I Intermittently	Type III Intermittently
COPROPORPHYRINURIA		NEGATIVE	NEGATIVE	Types I and III

TABLE I

SUMMARY OF THE URINARY PORPHYRIN EXCRETION IN THE PORPHYRIAS

infection processes such as pneumonia. Porphobilinogen is usually present in the urine of symptomatic cases of acute intermittent porphyria, present intermittently

in latent porphyria and may be present in mixed porphyria. It is not present in porphyria cutanea tarda and porphyria erythropoietica. All the forms of porphyria hepatica may show coproporphyrin III and a uroporphyrin which is usually referred to as Waldenstrom's uroporphyrin and is probably uroporphyrin type I, although it is claimed by others to be type III. Uroporphyrin I is found in the urine of porphyria erythropoietica. Regarding the color of the urine, grossly, it is usually thought that the urine must be colored to suggest a diagnosis; though actually porphobilinogen is colorless and the other porphyrins excreted will color urine only when excreted in large quantities such as in porphyria erythropoietica. From a practical standpoint then, a normal colored urine does not exclude the diagnosis of porphyria.

From the standpoint of treatment, splenectomy and protection from the sun in the porphyria erythropoietica are indicated, and screening from the sun would be indicated in the porphyria cutanea tarda. For the varied manifestations of acute intermittent porphyria in the form of abdominal neurologic or psychic symptoms, a wide variety of agents has been tried, and it is probably more important to know what not to give these patients. Alcohol and barbiturates are definitely contraindicated since they have been reported to precipitate an episode of porphyria.[5] For the relief of pain and sedation, Demerol, Chloral Hydrate and Paraldehyde are effective and apparently do no harm. At various times intravenous calcium, crude liver extract, Tetraethyl-ammonium Chloride, Cortisone and ACTH have been recommended, all with varying degrees of success. Chlorpromazine has recently been reported to be helpful.[6] Schrumpf[7] and Peters[8] have reported good results in the treatment of acute intermittent porphyria with BAL (Dimercaprol). Peters noted in some of his cases that an increased amount of zinc was present in the urine. BAL was given in an attempt to aid in the excretion of the zinc. The chelating agent disodium calcium versenate has been recommended and apparently may be effective on a similar process. An increased amount of zinc may be important in producing an enzyme lesion possibly by blocking to some extent the transformation of the porphobilinogen to the purines. BAL was chosen as the agent to be tried in the case of acute intermittent porphyria now to be discussed.

Patient (LH) a 43 year old, white housewife was admitted to another hospital on February 9, 1957, complaining of mid-abdominal pain which had been present for 2 days and was associated with nausea and constipation. The past medical history was negative. The pain persisted for 6 days, requiring narcotics at regular intervals. The pain disappeared then but was followed by development of pain in the legs and progressive weakness of the arms and legs. A Watson test for porphobilinogen was positive and the patient was transferred to Henry Ford Hospital on February 21, 1957.

The physical examination on admittance here was normal except for the neurologic findings. The patient was extremely lethargic. She would respond briefly to questioning but was unable to remain alert for any sustained period. There was a flaccid quadriplegia, and brain stem involvement was present with facial diplegia, ocular weakness and dysphagia. Sensation appeared intact.

On admission the urine was dark brown, gave a yellowish green fluorescence under a Wood's lamp and was positive for porphobilinogen. The hemoglobin was 12.8 grams, white count 12,200. Spinal fluid was negative except for slightly elevated protein of 57 mgm%. No cells were seen in the spinal fluid. An electroencephalogram showed a diffuse depression of electrical activity. Skull x-rays were negative.

The patient was started on BAL in a dose of 100 mgm every eight hours on February 23, 1957. An elective tracheotomy was done for retained secretions, and the patient was also begun on tube feeding via the Barron pump. Within 24 hours the patient was able to converse with the attending physicians and even stated a desire to go home, although the paralysis remained as before. She remained on BAL until March 15, 1957. During this period she was also given Chlorpromazine 25 mgm every 6 hours, as necessary, for moderate extremity pain which she was experiencing. The muscle power in the extremities gradually improved until discharged on April 13, 1957. At that

time the patient was getting out of bed in a chair for short periods and was noting increasing ability to move the extremities and had begun to feed herself.

The important aspects of physiotherapy and measures for rehabilitation in this patient were conducted throughout her hospital stay by Dr. William Schaefer and his staff in the Division of Physical Medicine and Rehabilitation.

Other laboratory data accumulated during the patient's illness were reported as follows: Cephalin cholesterol 1 plus, thymol turbidity 1 plus, thymol floculation negative, zinc sulfate 7 units, serum sodium 128 milli-equivalents per liter, serum chloride 106 milli-equivalents per liter, uric acid on two occasions was 1.3 mgm % and 2.2 mgm % and a 24 hour urine uric acid was 547 mgm (normal equals 500 mgm to 1000 mgm a day). The low figures for serum uric acid and 24 hour uric acid excretion lends some credence to the hypothesis that porphyria represents a block in the conversion of delta-aminolevulinic acid metabolism towards the purine metabolism. BSP showed 17% retention at 45 minutes, serum bilirubin a total of 0.5 mgm %, direct 0.125 mgm %. The sed rate was 2. Urinalysis was negative, non-protein nitrogen 28 mgm %, direct and indirect Coombs tests were negative, prothrombin time 16 seconds 90%, reticulocyte count 6%. Electrocardiograph was normal except for sinus tachycardia, and chest x-rays were negative.

On February 25, 1957, the 24 hour urine contained 21.8 mgm of porphobilinogen, 6000 micrograms of coproporphyin and 1750 micrograms of uroporphyrin. Daily quantitative determinations of porphobilinogen and coproporphyrin were done until March 2, 1957, and the quantity of these two compounds fell slowly so that on March 2nd the urine contained only 1.8 mgm of porphobilinogen and 1,680 micrograms of coproporphyrin. No further determinations of coproporphyrin were made, but the quantity of porphobilinogen continued to fall until it was absent within three weeks after admission and remained absent for the remainder of her hospital course. The urine color varied from dark brown to light straw. There was no appreciable change with exposure to light.

A niece of the patient gave a history of a very similar illness diagnosed as acute intermittent porphyria several years ago. The niece furnished a 24 hour urine for tesing, and it gave a positive reaction for porphobilinogen. The niece had no symptoms at that time, but interestingly enough, the patient who was bedridden by the same disorder was then passing urine which was negative for porphobilinogen.

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CONTRAINDICATIONS TO THERAPY IN* HYPERTENSION AND ANEMIA

ROBERT K. NIXON, M.D.**

In an era of ever-increasing medicaments for the ills of mankind, any appeal for consideration of less treatment must indeed sound anachronistic. Nonetheless, an occasional reaffirmation of the ageless hippocratic warning "primum non nocere" is felt to be justified in this hectic period of therapeutic innovations. In our enthusiasm for the new, a calm appraisal of what we are treating and what we can expect to accomplish by our treatment must continue to be the basis of all therapeutic thinking. All of us are intrigued with the unusual entities; the rare disorder is the challenge and the spice of medicine. However, the proper management of such ordinary conditions as hypertension and anemia may just as truly distinguish the capable physician as his handling of the obscure, involved diagnostic problem.

There is little doubt that man has always been endowed with a blood pressure. Whether the relatively recent ability to measure this particular physical fact has been a universal blessing may be seriously questioned. The morbidity engendered by the sphygmomanometer undoubtedly ranks high with that of other alleged boons of the machine age. The latter was supposed to free man — but this particular product, the blood pressure cuff, has probably harnessed more people to more grief and expense than we will ever know. As with all potentially useful tools, the failure has not been in the instrument but in the user, the physician himself.

The distinction between high blood pressure or arterial hypertension and hypertensive vascular disease is a vital and most important one. The former indicates an apparent abnormality requiring consideration and guarded follow-up; the latter represents an outright disease state necessitating active treatment whatever its etiology. High blood pressure is common and represents a threat, primarily because of the patient's awareness of having it. Hypertensive vascular disease is far less common and represents a true organic threat to the individual inasmuch as it portends a shortened life span. The responsibility for the confusion of the two conditions must be laid at the feet of the medical profession. Needless to say, the resolution of the confusion is our duty.

Thus, the question of whether we are dealing with simple high blood pressure or true hypertensive disease has much more than academic significance. Aside from the psychological burden to the patient which the diagnosis of hypertensive disease entails, the program of treatment with the agents currently available commits him to an indefinite period of considerable expense and no little hazard. The undesirable side effects of even the simplest antihypertensive medication — the Rauwolfia compounds — let alone the treacherous vagaries of the more potent Apresoline and ganglion blocking agents — should spur caution in our approach to treatment of what may be simple arterial hypertension.

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**Division of General Medicine.

What factors then should guide us in deciding this question of treatment, or to put the question another way, how do we decide whether the patient has high blood pressure or hypertensive vascular disease?

Studies have indicated that blood pressure is influenced by age,[1,2] sex and weight. Authorities differ about the limits of systolic pressure but most are in agreement that a diastolic pressure of 110 is abnormally high.

Master[1] has made an important contribution in his study of the effects of sex and age. He has concluded that for a man 20 years old, upper normal blood pressure limits are 140/88 mm Hg. Hypertension at 20 years of age exists with a systolic over 150 mm Hg and diastolic over 95 mm Hg. The significance of the range between 140-150 mm Hg systolic and between 88-95 mm Hg diastolic can only be determined with careful follow-up observations. At the age of 40, hypertension is said to be present with a systolic of 158 mm Hg and diastolic of 100 mm Hg. At 60 years of age upper limits are set at 180 mm Hg systolic and 110 mm Hg diastolic. Master and associates found that blood pressures for women are in general higher than in men after the age of 20.

The influence of obesity on hypertension and the frequent beneficial effects of simple weight reduction are familiar facts to all of us. It should be kept in mind that considerable error may exist in blood pressure readings taken on the obese arm. Recently, the taking of a blood pressure with the cuff on the forearm and auscultating over the radial artery at the wrist has been recommended as much more accurate in the obese patient. A limited personal experience would seem to bear this out.

Pickering[2] differs with most authorities in doubting that a definite dividing limit between normal and pathological blood pressure levels can be set. When one further considers the observations of Wakefield[3] in older women, this doubt is given further substance. He has studied some 500 female patients in the age group 70-100 over a 20 year span.

Seventy-five per cent of these patients at all times had essential hypertension with ranges of systolic pressures to 260 mm Hg and diastolic to 150 mm Hg. Many began with elevated blood pressure in the third and fourth decades and ran courses of 30 to 60 years duration. One lady, observed to her ninety-sixth year, carried a blood pressure of 260/140 mm Hg. The only treatment these ladies received during this twenty year period was encouragement and reassurance. Not a single patient manifested renal failure or severe nitrogen retention and careful study of the eyegrounds revealed, for the most part, only low grade arteriosclerosis. Wakefield could find no correlation of symptoms or blood pressure levels nor did hypertension seem to affect the rate of progression of other disorders or the subsequent development of complications.

One of several cases of this type under our observation is an 83 year old lady who was first seen in 1941 at the age of 67. Her blood pressure at that time was 200/100 mm Hg. Through the years it has been recorded as high as 260/140 mm Hg, averaging 200-220/100-110 mm Hg. In the past 16 years she has survived surgical fixation of a fractured hip, small bowel resection for obstruction due to a fibroma with intussusception, and, sad to relate, her original physician, who was

many years her junior. During these years there has been no change in her retinal findings, cardiac size, electrocardiograms, urinalysis or nitrogen retention. Her main setbacks, aside from the foregoing surgical procedures, have occurred when well meaning but futile drug therapies were attempted. In one instance, digitalis was given because of the development of basal rales which subsequently proved to be due to chornic bronchitis, not heart failure. With the advent of Rauwolfia drugs, it was inescapable that she be given a trial; the only effect was repeated bouts of diarrhea. At the present time she is leading an active, useful life and gradually recovering from her long-standing fear of high blood pressure.

It is apparent, then, that elevated blood pressure in itself is not an indication for drug therapy. In the absence of overt signs of cerebral, retinal cardiac or renal abnormality compatible with disease due to hypertension, no treatment is justified beyond simple reassurance for those patients who are unfortunately aware of it and premeditated failure to inform the others of its presence.

If criticism is to be leveled at our management of blood pressure, how much more vulnerable is our approach to that which is under pressure, the blood itself. In this realm, of course, anemia is the commonest stumbling block. No other entity subject to objective evaluation is probably as frequent in occurrence nor as often maltreated or overtreated.

In the problem of anemia, as with blood pressure, we are faced first of all with the same task, i.e., interpreting physical measurements with regard to the patient, his symptoms and his findings. Do the figures presented to us for RBC counts, hemoglobin and hematocrit constitute a pathological deficiency and if so, what is the cause?

It may be said that "anemia", in many instances, has about as much validity as so-called low blood pressure. Not uncommonly one sees patients with red cell and hemoglobin determinations in the range of fifteen per cent below the accepted lower normal limits; i.e., in women a red cell count of approximately 3.7 million and hemoglobin of 10 grams, with corresponding figures slightly higher in the male. These patients may have been observed over long periods and despite multiple functional complaints (including usually tiredness, weakness, etc.) and multiple hematinic treatments, their sound physical status and hematologic data remain unchanged. Extensive laboratory examinations disclose no other abnormalities.

An example in point is the case of a 59 year old colored female who has been observed and extensively examined for the past 15 years. On the basis of hemoglobin values consistently between 10 and 12 gm per 100 c.c., she has been plied continuously with iron, liver, vitamins and thyroid. Her many functional complaints of the neurasthenic variety have remained unaltered, as have her hematologic values. The morphology of her red cells, it should be stressed, is entirely normal.

Is this patient and many others we encounter in this category truly anemic? Should they be treated? Considerable light has been thrown on this type of problem by such studies as those of Nelson and Boyle[4]. They have shown in a group of 13 patients, some of whom — the females — had hemoglobins as low as 9.5 gms per 100 c.c., hematocrits as low as 34 percent, that the total circulating red cell mass was

normal but that the plasma volumes were relatively or absolutely increased. Thus, these patients were not actually anemic but by virtue of an increase in the fluid portion of the blood, an apparent anemia was suggested as judged by routine blood determinations. Obviously, no amount of hematinics can alter this deceptive, but in reality, normal condition. Various designations have been applied to these patients. Dameshek[5] terms them "anemia of neurasthenia"; others refer to it as dilution anemia or anemia of hypervolemia. The basic mechanism involved in the production of this disproportionate increase of plasma volume is not known but an awareness of this pseudo-anemia will help to avoid much totally unnecessary treatment.

Parenthetically, it is most interesting that the converse of this situation, that is, a pseudopolycythemia, equally subject to much confusion, exists on the basis of a decrease in plasma volume.[6]

Inasmuch as determinations of total blood volume and red cell mass are not as yet routine laboratory procedures, how can we avoid the pitfall of bland treatment of such patients for an "anemia" which is essentially an artefact? It goes without saying that the cornerstone of a careful and complete history and physical examination must be negative for pertinent abnormalities. Evidences of occult nitrogen retention, hypothyroidism, drug intoxications and chronic infections must be sought and excluded. With respect to the laboratory data, more reliance on hematocrit than hemoglobin is indicated, as the former will usually be less altered. A most careful analysis of the peripheral blood with particular reference to the morphology of the red cells is invaluable. The morphology of the red cells, I feel, remains entirely normal in those patients with pseudoanemia and if this is accurately ascertained by an experienced observer, it excludes most of the true anemias. I should like to underline this statement because this most basic examination of the blood smear for size, shape, hemoglobin content and hemoglobin maturity of the red cells properly done will give the clue to true or erroneous anemia in most instances. Unfortunately, few physicians are being trained these days to interpret the wealth of information available in the blood smear. Paradoxically, untold hours are given to mastery of the electrocardiogram waves — which is right and proper — but blood smears are too often relegated to technician personnel.

Granting, then, that treatment of pseudoanemia is contraindicated, what of the treatment of true anemia? Oddly enough, the answer should be the same — one never treats anemia. All of the current pharmaceutical huckstering for this or that multipurpose hematimic notwithstanding, anemia is a symptom, not a disease. Until the precise etiology is disclosed by logical step by step investigation, no treatment of the anemia is permissible. The one exception is that of acute hemorrhagic anemia where transfusions are sometimes required before the exact nature of the gastrointestinal lesion is disclosed.

Examples of the dire results of treating anemia as a symptom are too well known to this group to justify detailed recording. The cases of occult gastrointestinal neoplasms who are ineffectually treated by the "shotgun" method with subsequent tragic delay in the diagnosis of the underlying lesion; or the anemias due to bleeding from diaphragmatic hernias given the same all purpose hematinics made up of in-

sufficient amounts of the one needed element — iron; the pernicious anemia patients given preparations containing too much folic acid and inadequate B-12 who respond hematologically but relapse neurologically; anemias due to hemolysis, chronic infections, uremia, hypothyroidism or marrow replacing lesions carried unsuccessfully for months on all types of expensive drugs, delaying definitive diagnosis and management — all of these are well known to us and bear no further comment.

In the final analysis, both hypertension and anemia are symptoms. Failure to consider them as such may frequently lead to ineffective or unnecessary treatment. Knowledge of the physiological variations and pathophysiology involved with each will insure that specific therapy will be instituted only when indicated on the basis of an established disease state manifested by either of these symptoms.

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QUINCKE'S DISEASE

DORIS KAVANAGH M.D.*

Quincke's[1] disease has been known to the medical profession for at least 200 years. It was first differentiated from severe urticaria by Milton[2] in 1876 in a paper entitled "On Giant Urticaria". Six years later Quincke's paper on "Acute Circumscribed Edema of the Skin" attracted general attention. In it he presented his interpretation of the symptoms and the condition has since then borne his name. The term angioneurotic edema was introduced by Strübing[3] in 1885 and has been the name most commonly used to designate the condition since that time. Osler[4] in 1888 published an excellent description of the familial type — the least common form of angioneurotic edema. Until 1930 only 22 family histories had been described in the literature. However, since then many more such cases have been reported.[5,6,7]

The condition first makes its appearance in childhood, (it has been reported in a 56 hour old infant[8]) and usually persists throughout life. It is characterized by recurrent transient swellings of the skin, mucous membranes, or viscera. When involving the skin there is usually a sharp, stinging or itching sensation followed within a few minutes to hours by swelling which may rapidly progress to alarming proportions. The area is pale, cool, non-pitting, and is accompanied by a feeling of fullness. Itching and pain are usually absent. There is a strong tendency to recurrence especially in previously affected areas. When it effects the mucous membranes of the gastro-intestinal tract, crampy abdominal pain, nausea and vomiting may occur often accompanied by transient anuria. Almost immediate death may occur from edema of the larynx. A case in point was described by T. W. Griffith, of a young woman so affected. He writes, "Suddenly she started up, apparently tried to speak, clutched at her own neck . . . got blue in the face and died almost at once."[10] The viscera may also be involved. Crowder reported a case of an 18 year old girl with uterine involvement. Within 30 minutes the uterus "presented above the pelvis, as large, and to the touch very much the appearance of a 20 lb. cannon ball."[9]

Death commonly occurs from edema of the larynx. At autopsy the mucous membranes of the larynx are grossly edematous, pale, and translucent. The sides are usually in apposition, cutting off the airway. Some small amount of viscid mucous may be present. On microscopic examination the edema is found to affect the mucous membranes, deeper connective tissue, and even the substance of the muscles. The cells are chiefly of the mononuclear type. Occasionally the lungs have been reported affected, being voluminous and purple with pink frothy fluid exuding on pressure. The necropsy findings of such a case in a 14 month old child have been reported in detail by Wason.[11] Some patients with gastro-intestinal symptoms have come to surgery during the height of an attack. Two cases have been reported by Spaulding.[5] One, a 53 year old male, had 50 cm. of grossly edematous jejunum resected. The other case presented a considerable amount of fluid in the abdominal cavity, as well as large edematous lymph nodes in the mesentery of the small bowel. Barnett[6] reports of one patient operated for abdominal pain at McBurney's point, nausea and a leucocytosis

*From the Allergy Division.

of 22,000; 90 per cent of the cells were polymorphonuclear leucocytes. At surgery the peritoneal cavity was filled with pink staining fluid which coagulated on standing. The appendix was normal.

The mortality rate in affected members has been reported between 16 per cent by Fairbank and 51 per cent by Crowder.[9]

Quincke's disease is transmitted as a dominant trait under the Mendelian Law. Those individuals who escape in an affected family are not likely to transmit the disease while those affected transmit it to approximately half of their children. The mean age of death, usually, from edema of the larynx has been reported as 34.4 years. Thus death early in the reproductive years may account in part for the infrequency with which the disease is seen. The affected families tend to die out. Factors percipitating individual attacks are usually unknown. Pressure or trauma to a part may precede an attack. Excessive alcoholic intake or emotional stress in many cases may percipitate swelling. One would like to demonstrate a sensitizing agent in these cases, but that has not often been found and skin tests with foreign proteins have not proved helpful. Rarely the removal of a focus of infection, e.g. tonsils, teeth, has seemingly afforded temporary relief, lending a little support to the bacterial sensitization theory.

In general the treatment of Quincke's disease has been unsatisfactory. A host of medications have been tried without changing the course of the disease. Some of the treatments used and found ineffective are adrenalin, ACTH, cortisone, thyroid extract, antihistamines, elimination diets, desensitization programs, histamine, sedatives, vitamines, ultraviolet rays, etc. Sheldon reports that intravenous benadryl tended to abort some attacks when given early, but in other instances in which it was tried it had no effect. Tracheotomy is always indicated in laryngeal obstruction, and in some patients it has been necessary to repeat this procedure four or five times for repeated attacks.

Case Presentation:

Mr. W. C. has been followed at the Henry Ford Hospital for many years. His first attack of swelling, involving the lips, occurred at the age 14. From that time on he had repeated attacks of swelling, usually involving the lips, hands or neck. At the age of 26 he had his first attack of larynegeal edema and since then this has recurred several times a year.

His last admission was occasioned by one of his typical attacks, and will be reviewed in detail. On January 7, 1957 we contacted him requesting that he come to the clinic for protein testing the following day. He agreed but began to worry about the procedure and drank twelve cups of coffee. By 10 P.M. he felt nervous and noted a small area of swelling in the sub-occipital region. He awoke at 4 A.M., January 8, 1957, in respiratory distress and came to the hospital. He denied any alcoholic intake for 4 months prior to the attack. (It had been our impression that previous attacks were related to excessive alcoholic consumption.) On admission he was noted to be a slightly obese, white male, very apprehensive and appeared his stated age of 43. His temperature was 98.6, pulse 90, and respiration 24. The tissues of the neck were markedly swollen and pale, and the overlying skin appeared tense. His voice was hoarse and he was in mild respiratory distress. Laryngoscopic examination showed a pale, boggy swelling of the soft palate, uvula and tonsilar pillars. The larynx on this occasion appeared normal.

Treatment consisted of adrenalin, intravenous aminophylline, and 100 mg of hydrocortisone given intravenously. The attack began to subside about 12 Noon; 8 hours after awaking in respiratory distress, and it was over in 12 hours.

The patient's family history for angioneurotic edema is very interesting. His paternal grandfather had attacks of severe gastro-intestinal cramping all his life. The grandfather had four

children, 2 not affected, and 2 affected. The two affected members were the patient's father who had recurrent attacks of laryngeal edema and who died at the age of 55 of the disease, and the father's sister who also had attacks of laryngeal edema. The patient's father in turn had 2 children; the patient's brother, who is not affected, and the patient. The patient has 5 small children the oldest of which is 12. At present only one child seems affected, a 7 year old daughter with recurrent bouts of gastrointestinal distress, and swelling of the dorsum of the hands.

Summary:

(1) Available literature on the clinical entity known as Quincke's disease has been reviewed.

(2) A patient with Quincke's disease in which there is a strong hereditary pattern has been presented.

(3) Treatment for Quincke's disease to date has been quite unsatisfactory. We had hoped that this condition would be helped by the use of steroid preparations. To date reports in the literature on the use of steroids, and their use during 3 attacks in our patient have not been too encouraging. Further observation and treatment with these newer therapeutic agents would seem necessary before their true value can be ascertained.

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QUESTIONS AND ANSWERS ABOUT TOLBUTAMIDE, THE ORAL HYPOGLYCEMIC AGENT

FRED W. WHITEHOUSE, M.D.* AND JOHN B. BRYAN, M.D.*

When insulin was found to be ineffective by mouth, attention was given to the development of an orally effective hypoglycemic agent. Many compounds have been tested over the years. Most have been too toxic for clinical use.

Janbon in 1942 first described the hypoglycemic action of sulfonamide compounds.[1] Recently, modified preparations have been studied intensively in Germany and the United States. One preparation, carbutamide, proved to be too toxic for general clinical use. Tolbutamide†, a closely related compound, has proven to be relatively safe and has been made available throughout this country for the treatment of diabetes mellitus.

This report summarizes our experience with this agent and attempts to clarify questions that have arisen with its use. Recent reports afford the interested reader a more detailed analysis of its pharmacology and clinical use and an excellent bibliography.[2,3,4]

Question: What is tolbutamide?

Answer: It is a sulfonylurea compound that has a significant hypoglycemic action when taken by mouth.

Question: How does tolbutamide act?

Answer: Current opinions suggest multiphasic activity. Insulin must be present for an effect. Experimental evidence indicates that tolbutamide (1) causes either a production of or a release of insulin from the beta cells of the pancreas, (2) inhibits anti-insulin factors (insulinase) in the liver, (3) slows the release of glucose from the liver. Tolbutamide has no effect on other endocrine organs nor does it increase glucose uptake by the individual cell. Its action is not inhibited by ablation of the pituitary, thyroid or adrenal glands. There is no toxic effect on the alpha cells of the pancreas. It must be emphasized that the final and possibly correct modus operandi of tolbutamide has not yet been established.

Question: Is there a hypoglycemic effect in all diabetics as is true with insulin?

Answer: No. Animals following total pancreatectomy or alloxanization show no hypoglycemic effect. In humans the percentage of patients with a significant hypoglycemic effect closely parallels the percentage of patients with insulin extractable from the pancreas. Those patients without extractable insulin do not respond to tolbutamide.

Question: Is tolbutamide effective in diabetic acidosis?

Answer: No Neither is it effective in other acute complications of diabetes, including infections and surgical stress.

*Division of Metabolism.
†Orinase R — Upjohn Company, Kalamazoo, Michigan.

Question: What are the indications and contra-indications for its use?

Answer: Table 1 indicates our current opinion based on over a year's clinical experience. These indications are generally true, although there may be exceptions. They are to be used as a guide when applied to the individual patient.

Table 1

Indications	Contra-indications
Diabetes less than 10 years' duration.	Diabetes over 10 years' duration.
Onset of diabetes over age 40.	Onset under age 40.
Adult type diabetes.	Juvenile type diabetes.
Diabetes controlled with *less* than 30 units of insulin daily.	Diabetes controlled with *more* than 30 units of insulin daily.
Cooperative patient.	Uncooperative patient.
	Acute complications.
	Ketosis.

The presence of one contra-indication is sufficient to disqualify a patient for tolbutamide therapy. Tolbutamide is an insulin substitute clinically. It is not indicated in the obese diabetic patient before an adequate trial with undernutrition has been accomplished. Only if weight loss does not occur, or if not successful in controlling the diabetes, should tolbutamide be considered.

Question: What are the side-effects of tolbutamide?

Answer: We have seen one case of dermatitis and one case of nausea and vomiting, requiring cessation of the drug, in 150 cases treated with tolbutamide. There may be transient leukopenia, but no other hematologic complications have been encountered. Crystalluria does not occur. We have experienced no hepatic dysfunction. O'Donovan[5] reports three percent side-effects in over 7000 clinical cases. These have all been mild. There are no known deaths directly attributable to tolbutamide.

Question: How is a patient regulated with tolbutamide?

Answer: Once a decision to use tolbutamide is made, initiation may be accomplished either in the hospital or with frequent office visits. Hospitalization is recommended if there is any question regarding the patient's likelihood of response. The following program has been generally adopted in our clinic:

1. Begin with 1 gram 3 times daily.
2. After 1-3 days, decrease to 1 gram twice daily.
3. Adjust the daily maintenance dosage with the help of frequent urine tests and blood tests for sugar.
4. If the patient is on insulin at the time of initiation,
   a. omit insulin if less than 20 units per day.
   b. If over 20 units daily, decrease the daily dose 25-50 percent initially, and then eliminate the insulin if the blood sugars so indicate.
5. Check the white blood count frequently at the beginning of therapy.

Question: How long should one await a successful response?

Answer: Not longer than 7-10 days. If the degree of diabetic control deteriorates sooner, abandon the trial at once and start insulin. The development of ketonuria indicates failure. It is imperative that the patient be kept under close observation during this trial period.

Question: What is the average maintenance dose?

Answer: Table 2 records the maintenance dosage of 83 patients regulated on tolbutamide.

Table 2
Maintenance Dosage of Tolbutamide

Grams per day	Number of patients
0.5	8
1.0	23
1.5	14
2.0	24
3.0	14

Question: Can tolbutamide and insulin be used together?

Answer: Yes, but there is little point in it. The only advantage of tolbutamide over insulin is its effectiveness by mouth. Theoretically, one might lower a very large daily dose of insulin to a more convenient level with the aid of tolbutamide. We have tried this twice without success.

Question: Should tolbutamide be used in the obese diabetic patient?

Answer: Tolbutamide, like insulin, is contra-indicated initially in the obese diabetic patient. Undernutrition should be tried first. If optimum weight is accomplished and still the diabetes is not controlled, then tolbutamide may be tried. If poor cooperation prevents weight loss, then tolbutamide probably should also be avoided.

Question: Can the diet be liberalized when tolbutamide is used?

Answer: No. If anything, it should be followed more closely.

Question: Once on tolbutamide, must the patient stay on it?

Answer: Like insulin, no. A patient with mild diabetes and good control may improve his glucose tolerance to the degree that diet alone will adequately control his diabetes.

Question: If the patient is regulated on tolbutamide, will insulin again be necessary?

Answer: Most patients on tolbutamide will require insulin if acute stress occurs. A few patients well regulated on tolbutamide at the beginning will gradually lose this good control. They must restart insulin.

Question: How is tolbutamide supplied?

Answer: Half-gram tablets, bottles of 50, $6.75 per bottle, filled by prescription only.

Question: Does tolbutamide have any antibacterial activity?

Answer: No.

Question: Has hypoglycemia been a problem?

Answer: No. We have seen no serious hypoglycemic reactions. There have been several mild reactions occurring during the first few days following initiation of tolbutamide therapy.

Question: What have been the failures?

Answer: Our failures with the use of tolbutamide include patients with diabetes and carcinoma of the pancreas (4 cases), steroid diabetes (1 case) and juvenile type diabetes. The basic nature of the diabetes appears to be the most important determinant in the individual response to tolbutamide.

Question: What theoretical danger exists with the use of tolbutamide?

Answer: Permanent diabetes can be produced in animals by chronic overstimulation of the beta cells of the pancreas. Tolbutamide is a beta cell stimulator. Will tolbutamide in time produce "total" diabetes in patients maintained on it?

A patient with diabetes well regulated with tolbutamide will lose this sensitivity in the presence of acute complications. This may make the patient more vulnerable to the rapid occurrence of ketosis and acidosis than a similar patient regulated with insulin.

Summary:

The experience at the Henry Ford Hospital with tolbutamide is reviewed. Pertinent questions regarding its use are answered. The only advantage of tolbutamide over insulin is one of convenience — it is effective orally. The present and future health of the diabetic must not be compromised for mere convenience. The patients using tolbutamide must be carefully and thoughtfully selected.

We are grateful to Doctor C. J. O'Donovan of the Upjohn Company, Kalamazoo, for the generous supply of tolbutamide.

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ANAPHYLACTOID REACTION TO ORAL PENICILLIN G; CASE REPORT

ROBERT E. BIRK, M.D.,* AND EDWARD L. QUINN, M.D.**

Of the possible reactions to penicillin, the most dangerous is anaphylactic shock. Most anaphylactic reactions reported have been due to procaine penicillin administered parenterally.[1] Anaphylactic reactions can, however, occur with orally administered penicillin. In a recent summary of recorded cases of anaphylactic reactions to oral penicillin, Maganzini[1] collected a total of eleven cases with one death.

Reactions to orally administered penicillin have been reported to occur less frequently than to parenterally administered penicillin.[2,6] The incidence of reactions of all types to orally administered penicillin has been noted to be 0.2 to 2.0 percent.[7,9] In contrast, reactions following parenteral administration of penicillin can be expected to occur in 2 to 2.5 percent of children,[2,10] 5 percent of non-allergic adults, and 15 percent of allergic adults.[11]

A case report of an anaphylactic reaction following the ingestion of oral penicillin G is presented.

Case Report

E. K., Henry Ford Hospital Case Number 78 01 79, a twenty-five year old white male dishwasher, was admitted to the Emergency Room at 10:30 A.M. on May 24, 1955. He was first seen leaning against the receiving desk, vomiting and unable to talk. The initial history was obtained from a friend. He was reported to have developed a pruritic, erythematous rash over his face, chest, arms and legs, accompanied by a complaint of weakness, thirty minutes prior to admission. Fifteen minutes later he vomited clear fluid and the remnants of a sandwich eaten one hour before.

Physical Examination: The temperature was 97.6° F., pulse 100 per minute, respirations 20 per minute, blood pressure 40/0 mm. of Hg. There was a diffuse, macular, erythematous rash on the face, chest, arms and legs which blanched on pressure. The patient was vomiting and retching violently and was perspiring profusely. The chest was clear to percussion and auscultation. The heart was rapid with regular rate. There was minimal epigastric tenderness. The examination was otherwise essentially negative.

Hospital course: He was given 0.1 mgm. of epinephrin hydrochloride subcutaneously and 1000 cc. of 5 percent glucose in water was started intravenously. Ten minutes later, the blood pressure was 90/60 mm. of Hg. Hydrocortisone, 100 mgm. in 1000 cc. of 5 percent glucose in physiological saline, was started intravenously at this time. At 11:00 A.M. the blood pressure was 60/0 mm. of Hg. and 4 cc. of 0.1 percent levarterenol bitartrate (Levophed) were added to the 1000 cc. of 5 percent glucose in water. One hour after admission, the blood pressure was 100/60 mm. of Hg., and subsequently remained normal. As the blood pressure rose towards normal, the patient became responsive and was able to relate pertinent history.

At this time he stated that he had sustained a laceration of the hand on May 7, 1955 which was treated with one injection of 300,000 units of procaine penicillin G and oral penicillin G tablets which he had taken sporadically up to one week prior to admission. He had ingested a single tablet of 200,000 units of penicillin G thirty minutes prior to the onset of the present illness. There was no past history of allergic reaction or previous penicillin sensitivity.

Subsequent treatment consisted of hydrocortisone orally for fourteen days, beginning at 80 mgm. daily with gradual reduction to 30 mgm. daily.

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*Associate Physician, Medical Clinic Number Four.
**Physician-in-charge, Division of Infectious Disease.

Except for marked asthenia and two transient febrile episodes during the first three days of hospitalization, he was asymptomatic and remained so following discharge. He was last seen on August 15, 1955 for an unrelated complaint. There had been no further symptoms related to the recent illness.

Laboratory examination: May 24, 1955: White blood count 15,700 per cu.mm. with 89 percent neutrophils, 10 percent lymphocytes and 1 percent monocytes. Urinalysis: specific gravity 1012, alkaline reaction, albumin negative, Benedict's reaction three plus, acetone negative. (This specimen was obtained during intravenous glucose administration.)

May 25, 1955: Hemoglobin 14.6 gms. percent. White blood count 16,470 per cu.mm. with 81 percent neutrophils and 19 percent lymphocytes. Sedimentation rate 7 mm. per hour (Wintrobe). Fasting blood sugar 97 mgm. percent. Non protein nitrogen 36 mgm. percent. Kline exclusion test negative.

Summary

The case reported represents a typical anaphylactic reaction to penicillin.

The etiology of the reaction was unknown at the onset of therapy because of the inability of the patient to give an adequate history. The findings of a generalized pruritic erythematous rash and signs of vascular collapse led to the institution of therapy for anaphylactic shock.

It is generally accepted that reactions are less frequent following oral than parenteral administration of penicillin, but it is important to emphasize that anaphylactic reactions may occur following orally administered penicillin.

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USE OF RADIOACTIVE COLLOIDAL GOLD (AU198) IN TREATMENT OF CARCINOMA OF THE CERVIX

ELLERY T. DRAKE, M.D.*

Historical: In 1851, Charles C. Meigs[1] wrote that a diagnosis of cancer of the uterus was a prognosis of death. Even now, the state of our knowledge of the treatment of carcinoma of the cervix leaves much to be desired.

The first surgical approach in the treatment of this disease consisted of a simple vaginal operation. Complete abdominal hysterectomy at a later date failed to remove the disease except in very early cases. Wertheim[2] after performing 500 radical hysterectomies reported his results and established a standardized operative procedure. Mortality was high with 93 deaths, 39 of wich were attributed to peritonitis. With the advent of x-ray and radium, surgery with its high mortality was rejected by all but a few pioneers. With accumulation of experience and improvements in technique it was still apparent, however, that deep x-ray therapy did not eliminate distant metastases in the pelvis.

Roentgen, as a result of his research work in Wurzburg, Germany, discovered the x-ray in 1895. This was followed in 1898 with the discovery of radium by Mme Curie. In 1901, Becquerel placed a tube of radium in the pocket of his coat and a week or two later, a severe inflammation appeared in the skin beneath the radium. Besnier examined the dermatitis and suggested the use of radium as a therapeutic agent. In 1903, Morton in New York first reported the treatment of fibroids by x-ray.

Just prior to the first World War, announcements that radium would cure cancer encouraged several institutions to purchase large amounts of the element. The value of radium in the treatment of gynecological conditions was first fully realized by Kelly of Baltimore. In 1915 he reported a large series of cases treated with radium.

Progress in Surgery: Blood replacement, sulfonamide drugs and antibiotics encouraged Meigs[3] to re-explore the possibilities of radical hysterectomy. Taussig[4] emphasized that careful, nearly en bloc dissections of nodes of the pelvis should be made. Wertheim removed these lymph glands only if they were palpably involved, which in some instances resulted in cancer being left in the pelvis if metastases were minute or microscopic. Meigs[5] combined bilateral pelvic lymph node dissection with radical hysterectomy and in 1951 reported a series of 85 cases which stimulated interest again in the surgical approach to the problem. He cited the use of silver dura clips in node bearing areas as suggested by Dr. Langdon Parsons, and pointed out that effective radiation therapy was not being administered to the more distant nodal areas which were removed by surgery.

The occurrence of radioresistant tumors which extend locally prior to the development of distal metastases prompted Brunschwig[6] to effectively increase the extent of radical surgery. Many cases, however, which recur after radiation or radiation and surgery present widespread dissemination and are hopeless with any form of treatment.

Progress in Radiotherapy: Morris and Meigs[7] admitted that their results with radiation therapy were unsatisfactory even though they were comparable to the figures from

*Department of Surgery.

other clinics. Studies with ionization chambers in the cervix revealed that the tumor dose of radiation was often far different from the calculated dosage in air. Calculations of isodose curves often showed that distal extensions of a tumor did not receive cancerocidal doses from the radium given. Increased accuracy of measurement of radiation in gamma roentgens at the periphery of the tumor is desired. It is a more accurate statement of effective dosage than measurement in milligram hours. Volume of tissue radiated, uniformity of the tissue radiation and physical distribution of the source together with improved methods for clinically determining the exact extent of the tumor are problems to be faced.

With an increase in the safety of radical surgery, ready access to lymph nodes of the pelvis has aided in the study of the effects of radiation. Reliable methods of quantitating the radiant energy delivered have aided in standardization of therapeutic schedules.

Recurrences after surgery or radiation are frequently found in the lateral pelvic wall suggesting that tumor cells were already outside the effective area of irradiation or operation at the time of treatment. Current thought is therefore being directed toward more efficient treatment of the lateral pelvic wall.

Results of Current Therapy: Complete hysterectomy will cure practically all cases of carcinoma in situ with no need for irradiation. In Stage I lesions a cure rate of 70 to 80 per cent is possible by either radiotherapy or surgical operation. The cure rate is about 50 per cent by either method of treatment when Stage II lesions are considered. With more extensive lesions, radiotherapy probably has more to offer. We are faced with the fact that two-thirds of all women presenting themselves for treatment of carcinoma of the cervix still die within five years from local extension of the tumor or distal metastases.

Radioactive Colloidal Gold (Au198): With the advent of the atomic age and the construction of the nuclear reactor pile, radioisotopes became available for clinical investigation.

Radioactive colloidal gold (Au198) is an isotope prepared by neutron bombardment of gold foil in a nuclear reactor pile. It is converted to gold chloride and is then reduced to metallic gold by ascorbic acid in the presence of excess gelatin. In this form, it is a stable colloid with deep cherry red color. With decay it is converted to the end product mercury (Hg198).

Particle size of the gold in suspension varies from 0.001 to 0.003 microns. The suspension of colloidal gold contains 10 trillion particles in 50 mc with each particle acting as a source of radiation. It has a half life of 2.7 days which allows about 95 per cent of the radiation dose to be delivered in 11 days. The radioactivity is due essentially to a 0.97 mev beta ray which has a maximum range of only 3.8 mm. in water and a 0.411 mev gamma component. It is reasonably heat stable.

Early Observations: In 1946, Sheppard and Hahn[8] called attention to the fact that radioactive isotopes were of most therapeutic value when there was some selectivity of uptake by the tissues. This selectivity is shown by the uptake of radioactive iodine

by the thyroid and by the uptake of radioactive strontium by growing bone tissue similar to its uptake of calcium. In addition to this natural selectivity, uptake by the tissues is also determined by the method of preparation, and the route of administration.

Drinker and Shaw[9] found that as much as 90 per cent of particles almost colloidal in size were taken up by phagocytic cells of the liver when the preparation was given intravenously.

Colloidal sols of radioactive manganese (Mn52) and gold (Au198) were studied by Sheppard, Wells, Hahn and Goodell[10]. These isotopes were given by cubital vein to several patients whose disease terminated fatally. Radioactivity of various tissues at autopsy was measured and compared. The liver and spleen contained a high concentration of radioactive gold with an intermediate concentration in the kidney and a low concentration in other organs.

Radioactive colloidal gold emits a gamma ray which makes it possible to determine the distribution of the injected material with a collimated counter. By the use of a directional type of counter, Jones, Wrobel, and Lyons[11] found that radioactive material remained in the tissues in which it had been deposited for as long as measurements could be made. Insolubility of gold colloids in body fluids suggested that they could be used for direct infiltration of neoplastic tissues[12]. Lymphomas and carcinomatous tumors in human subjects were treated by injections of radioactive gold directly into the tumors.

Some tumor tissue was so friable that it would not retain even small amounts of fluid. Other tumors were so vascular that local injection was tantamount to intravenous infusion.

Injection of tumors deep in the body precludes the need of excessive radiation of normal tissues to obtain an effective dose in the tumor. After injection of the tumor, the greatest intensity of radiation is within the tumor, decreasing toward the normal tissue in the periphery.

The radiation effect produced in tissues is almost entirely due to the beta emission. Because of a short half life of 2.7 days, it is unnecessary to remove the applicator supplying the source of radiation as is the case with radium.

Insolubility of radioactive colloidal gold which exists in metallic form renders it chemically and biologically inert. It has none of the toxicity of gold salts.

Animal Experiments: Sherman, Nolan, and Allen[13] conducted experiments in mice to determine the effectiveness of radioactive gold in the treatment of squamous cell carcinoma by direct injection. They found that colloidal gold leaked from puncture points in the skin and that it was absorbed into the general circulation from injection sites. To overcome this, the gold was suspended in a solution of pectin and dextrose. It was found that these tumors in mice could be cured with high survival rates when 200 to 300 microcuries per cc. of tumor tissue were injected. One to 25 millicuries of radioactive colloidal gold in pectin solution were injected under direct vision into the parametria of rabbits through an abdominal incision. At reoperation, 72 hours later, it was found that lymphatic channels were increased in number and were filled

with phagocytic cells. Gold particles were contained in the cytoplasm of the scavenger cells. Seven days after injection, considerable amounts of gold were found in the iliac lymph nodes accompanied by marked radiation damage. The injected area at three months showed marked fibrosis and atrophy of the normal cellular structures. Lymphatic channels were lined with gold particles and were involved in the fibrotic process.

In a study of tissue tolerance to radioactive gold, injection of graded doses from 0.25 to 3.5 millicuries per cc. of parametrial tissue was made. There were no injurious effects to normal structures at therapeutic levels. A study of general and local tolerance levels for radioactive colloidal gold injected into the parametrium of the monkey was made by Nolan, Jones, and Neil[14]. They concluded that limitations imposed by necrosis at the site of injection rather than liver injury was the decisive factor in arriving at the proper dosage for the human subject. They inferred that if 25 to 50 millicuries were injected into each parametrium, there would be sufficient spread through the parametrium and pelvic lymph nodes to cause sclerosis without extensive necrosis.

Clinical Experiments: In consideration of the above results, Sherman, Bonebrake, and Allen, in 1951,[15] were encouraged to continue the experiments at a clinical level. They found with cadavers that 50 to 60 cc. of material could be injected easily into each parametrium through the vagina. A technique was devised which resembled the insertion of radium needles into the parametrium. With sterile precautions, a 22 gauge spinal needle was inserted laterally through the mucosa and Mackenrodt's ligaments. The needle was advanced and angled 20 to 30 degrees from the midline to approximate the pelvic wall. Once in position, the stylet was removed and gold was injected as the needle was slowly withdrawn to prevent pooling. Three sites were usually injected in each parametrium to give a uniform dispersion of the gold throughout the area to be treated.

Ten patients with carcinoma of the cervix were injected with radioactive colloidal gold in amounts sufficient only to be traced and located at operation. The parametrial areas, showed definite radiation effects with cellular destruction and accompanying fibrosis. There was a marked increase in lymphatics which were engorged with phagocytes containing gold particles. The blood vessels showed typical radiation effects of endarteritis. Definite localized radiation effects were present in the lymph nodes. Two cases were found to have cancer cells far out in the parametrial tissues. However, they were encircled by radioactive gold and showed the usual disintegrating changes associated with irradiation.

In 24 patients, Allen, Sherman, and Arneson[16] determined the amount of irradiation received by various lymph nodes removed at operation. Gamma radioactivity was measured with a scintillation counter and the total amount of beta irradiation was calculated. It was evident that most of the nodes removed received more irradiation than do those treated by present day x-ray and radium.

Diodrast was added to the radioactive solution. X-rays made after injections of 30 to 40 cc. in each side showed diffuse infiltration of the parametrium. Scintoscanner measurements made during a two week period after injection showed that radioactivity was unchanged except for anticipated decay.

Allen, Sherman, and Arneson[16,17] reported the clinical use of radioactive colloidal gold and seemed to have better results than in comparable cases treated with x-ray and radium. Veldhuis, Swinehart, and Preuss[18] also reported a series of cases with favorable results.

Toxic Effects: The use of radioactive colloidal gold is not innocuous. This is attested by an increasing number of reports of toxic effects in the literature. In laboratory animals liver damage[19], hepatomas[20], and cirrhosis with ascites[21] have been produced by radioactive gold administration. Weight loss, anorexia and pleural effusions with varying degrees of bone marrow hypoplasia and anemia occurred in dogs after intraperitoneal administration of radioactive colloidal gold.

In three clinical cases treated with transvaginal injections of radioactive gold, a skin rash was noticed. This was attributed to sensitivity to pectin contained in the solution[15].

Radiation sickness with nausea and vomiting has been reported. Intratumoral injection is accompanied by less radiation sickness than with the use of x-ray or radium because there is less radiation of normal tissues[22]. This may well be true with interstitial injection if vascular tissues are avoided.

Schoolman and Schwartz[23] reported a case of aplastic anemia following intravenous therapy with radiogold. Hypoplasia of bone marrow was reported by Botsford et al[24] in four patients who received a dose of more than 50 millicuries. Gold was present in bone marrow following intraperitoneal or intratumoral injections.

Any patient who has received injections of radioactive gold must be considered a hazard to attendants[25]. Excreta of patients following intratumoral injections have never shown any appreciable radioactivity.

Genitourinary fistulas were noted in three patients treated by transvaginal injection of radioactive gold[16]. These patients also received radium and radical surgery. No serious complications of this nature followed the use of radioactive gold and operation or radioactive gold and radium. A patient who developed an abdominal fistula after intraperitoneal injection of radioactive gold has been reported[26].

Paralysis may occur when radioactive gold is injected into or in close proximity to nerves[27].

COMMENT

The ultimate value of irradiation of pelvic lymph nodes has not been proven. Whether metastatic carcinoma in the pelvic lymph nodes may be destroyed by radiation or whether it is peculiarly resistant to this form of treatment is debatable. However, there is strong suggestive evidence that irradiation of pelvic lymph nodes is a worthwhile procedure in terms of five year survival of patients[28].

Extension of tumor from the cervix is usually by direct or lymphatic extension laterally along the uterine vessels and Mackenrodt's ligaments. Radioactive colloidal gold is injected parametrially anticipating that it will be carried by phagocytes along

the same lymphatic channels as the tumor cells. Once the lymphatic channels are blocked with tumor cells, phagocytes containing radioactive gold may be shunted through other channels. A cancerocidal dose of radiation may never reach the lymph nodes that are already engorged with tumor cells.

Clinical observations indicate that there are marked variations in radiosensitivity of cervical cancer. Early recognition of radioresistant tumors is desirable so that surgery can be recommended. Radiation-sensitivity testing has been studied with conventional histologic techniques[29], by cytologic changes[30] and by radioactive tracer methods[31].

Although there are undoubtedly relative degrees of radiation sensitivity, it is very likely that only a small percentage of cervical cancers are highly resistant. Central cervical cancer is usually well healed after x-ray or radium therapy even in patients who succumb from metastases. Even though intensive focal radiation of pelvic lymph nodes is possible after injection of radioactive gold, there undoubtedly will be some resistant tumors that will fail to respond to treatment.

The final appraisal of the clinical use of radioactive gold must await further observations of large groups of cases with adequate controls.

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A REASONABLE ATTITUDE TOWARD THE MEDICAL USE OF DIAGNOSTIC RADIATION

WILLIAM R. EYLER, M.D.* AND WENDELL M. BURNS, M.D.**

From the beginning of life man and his phylogenetic predecessors have been immersed in a sea of radiation. Indeed, it seems likely that the natural radioactivity at the level of the earth's crust has been steadily decreasing since the formation of the earth. Present concern with the effect of radiation upon humanity thus is a consideration not of a new agent, but rather of what effect a quantitative difference may cause.

The study of this field necessarily is divided into the problem of the effects of radiation on the individual and that of the genetic effects on the future of the race. The genetic aspect will be considered first.

In order to form an idea of the magnitude of this change in incident radiation and to form an idea of its relationship to what mankind has been receiving previously, the components of "natural" radiation will be examined.

The most penetrating radiation is that of cosmic rays, which deliver approximately 0.028 rad* per year.[3] Gamma radiation from our natural surroundings is highest in brick and concrete houses and certain buildings made of granite.[10] This delivers approximately 0.043 rad per year, but can go as high as 0.3 rad per year.[12] The activity due to radon in the air contributes 0.011 rad per year.[8]

Radiation from our own tissues is delivered by Potassium 40 (0.02 rad per year) Carbon 14 (0.001 rad per year) and Radon and its disintegration products in the tissues (0.002 rad per year).[8] The total dose per year is thus about 0.095 rads and the total dose to age 30 to either gonads or other tissues is approximately 2.85 rads.[8] Since the only radiation of genetic importance is that received prior to parenthood and the average age at parenthood is 30 years, the significant figure is the 30 year gonadal dose. This information is summarized in the accompanying Table I.[8]

Our current civilization imposes additional radiation upon the bone marrow and genes of mankind, the greatest source of which is without doubt the medical use of diagnostic roentgen examinations. The minimum estimates for the population dose of this radiation per year range from a low of 22 mr, arrived at in the area of Leeds[12] to estimates of 100 mr made for this country.[9] Radiation from fluoroscopic shoe fitting, luminous watches and clocks, television sets and high altitude flying are all small. Occupational exposure in radiology and industry and atomic energy personnel exposures contribute less than 2 mr per year;[8] this is summarized in Table II.

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*The rad is a unit of absorbed dose and thus a more biologically significant unit than the "r" or incident dose. Whenever possible rads will be used as the unit, but where no such data is available, the "r" will be used. 1 rad = 1000 millirad. 1 "r" = 1000 mr.

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*Radiologist-in-Chief.
**Resident in Radiology.

TABLE I. (TABLE 4J REPRODUCED FROM THE REPORT OF THE MEDICAL RESEARCH COUNCIL OF GREAT BRITAIN[8])

Dose-rates to the gonads for a region of 'normal' ground radioactivity

RADIATION SOURCE	DOSE TO GONADS PER YEAR (rad)
EXTERNAL IRRADIATION	
Cosmic rays (sea level)	0.028
Local gamma rays (Leeds, 78 millirad/year indoors	0.043
48 millirad/year out-of-doors	0.001
Radon in air, 3 x 10^{-13}c/1	
INTERNAL IRRADIATION	
Postassium 40	0.020
Carbon 14	0.001
Radon + disintegration products, 3 x 10^{-13}c/1	0.002
Total dose per year	0.095†
Dose to age 30 years	2.85 †

† Includes allowance for the R. B. E. of the alpha radiation where present, and therefore also expresses the gonad-dose in rem.

TABLE II. (TABLE 4 REPRODUCED FROM THE REPORT OF THE MEDICAL RESEARCH COUNCIL OF GREAT BRITAIN[8])

Summary of estimated population doses of radiation to the gonads expressed as percentages of natural background

SOURCE OF RADIATION	Approximate dose to gonads as a percentage of natural background
Natural background	100
Diagnostic radiology	at least 22
Radiotherapy	?
Shoe-fitting	0.1
Luminous watches and clocks	1
Television sets	much less than 1
High altitude flying	insignificant
Occupational exposure:	
Radiology and Industry	at least 1.6
Atomic Energy Authority	0.1
Fall-out from test explosions	less than 1

If weapons testing is continued at the rate of the last 5 years, the estimated yearly gonadal dose in this country is 3 mr, but if it were to proceed at the higher levels of 1953 and 1955 this dose would be multiplied[9] by 2. The total of these radiations is thus slightly above the natural background.

The application of radiation results in the acceleration of the evolutionary process and since more unfavorable mutations are produced than favorable ones, an increase in the process of natural selection results. The best estimate which can be made at this time of the dose of radiation which, if administered continuously to the entire population for 100 generations, would cause a doubling of the amount of clinically apparent mutation is 50 rads gonadal dose by age 30.[2,8,9] The one generation effect of this dose, however, would produce a barely detectable clinical increase in mutation, being of the order of 2-3%.[8,9] Roughly 4-5% of all live births in the United States have defects and of all these it is estimated that half or about 2% of the total of live births have defects of genetic origin.[9] Doubling mutation rates of both parents would add an additional 0.2% to the present chance of producing a defective child.

Though 50 rads is an acceptable dose for a very small fraction of the population, 10 rads is suggested as the top limit for the whole population.[8,9] The current dose is 4 rads. At present dose levels about 0.01% of the new generation or 1/10,000 bears some defect due to "civilization" radiation compared to 800/10,000 who are stillborn or malformed due to other causes.[8] The wide dispersion of latent mutations makes the average dose that the whole population receives the important figure, rather than dose to individuals.

The second aspect is the effect of radiation on the individual. Accidental exposures and exposures during time of war indicate that when a population is subjected to a dose between 400 and 600 r total body radiation half of them will succumb. At the other end of the time scale is the chronic small dose exposure received by those whose occupation brings them into contact with radium and x-ray. There is an increased mortality among radiologists due to leukemia, which indicates an examination of the relationship of leukemia to radiation. This has been done best by E. B. Lewis[5] who has correlated data from four groups of individuals. These groups are first, survivors of the atomic bomb radiation in Japan; second, patients radiated for ankylosing spondylitis; third, children radiated as infants for thymic enlargement and fourth, radiologists.

When one plots the incidence of leukemia among the survivors of Hiroshima and Nagasaki in comparison with the distance of the individuals from the hypocenter, and thus the dose which they received, one finds a relatively constant value for the probability of acquiring leukemia of 2×10^{-6} per individual per rad per year. Thus if an individual receives a total body dose of 100 rads, his chance of dying of leukemia is 200 out of a million.

Court Brown and Doll[8] have studied the incidence of leukemia among patients treated with x-rays for ankylosing spondylitis. Of 11,287 patients irradiated during the period of 1935 to 1954, 37 developed leukemia. In this situation as well, the dose

of radiation delivered to the red marrow increased the incidence of leukemia in proportional fashion and produced a remarkably similar value of probability of developing leukemia.

Simpson, Hemplemann and Fuller[11] traced 1,400 individual infants who had been given radiation for enlarged thymus and a control group of unirradiated siblings. In this group there were 7 confirmed cases of leukemia with none in the controls. The number of cases expected in this treated population is 0.6. This gives a remarkably similar probability value.[5]

March[6] called attention to the increased incidence of leukemia in radiologists in 1944, and at the time of his second report in 1950 had collected a total of 14 deaths. Subjecting this information to the same type of analysis, similar probability value is obtained.

Recent publicity in the public press has stressed the hazard of radiation and has neglected to consider the benefits derived from this type of medical examination. Asymptomatic individuals over the age of 50 show a 0.2% incidence of cancer alone.[13] At this time the hazards of neglecting proper roentgen diagnostic studies are considerably greater than the hazard of genetic damage or leukemia.

SUMMARY

1. The production of mutations by radiation absorbed by the gonads prior to parenthood is a linear function of the quantity of radiation without any evidence of a threshold effect.

2. The incidence of clinically apparent mutations induced at the present rate of utilization of diagnostic medical x-rays and present quantity of fall-out from nuclear explosions is predictable with considerable certainty as approximately 1/10,000 new births compared to 800/10,000 stillborn or malformed due to other causes.

3. Those procedures which produce a particularly high dose to the patient, such as pelvimetry, should be carefully re-evaluated both for possible improvements in technique and for indications.

4. The probability of an individual developing leukemia, in addition to the spontaneous incidence, appears to be a direct function of the amount of radiation absorbed by him, again without a threshold level, but with a linear relationship between radiation absorbed by the bone marrow and frequency of leukemia.

5. The advantage from diagnostic roentgen studies at the present time is far greater than the hazards of leukemia. The current publicity concerning radiation hazards has neglected to mention the considerable benefit to many patients from such studies.

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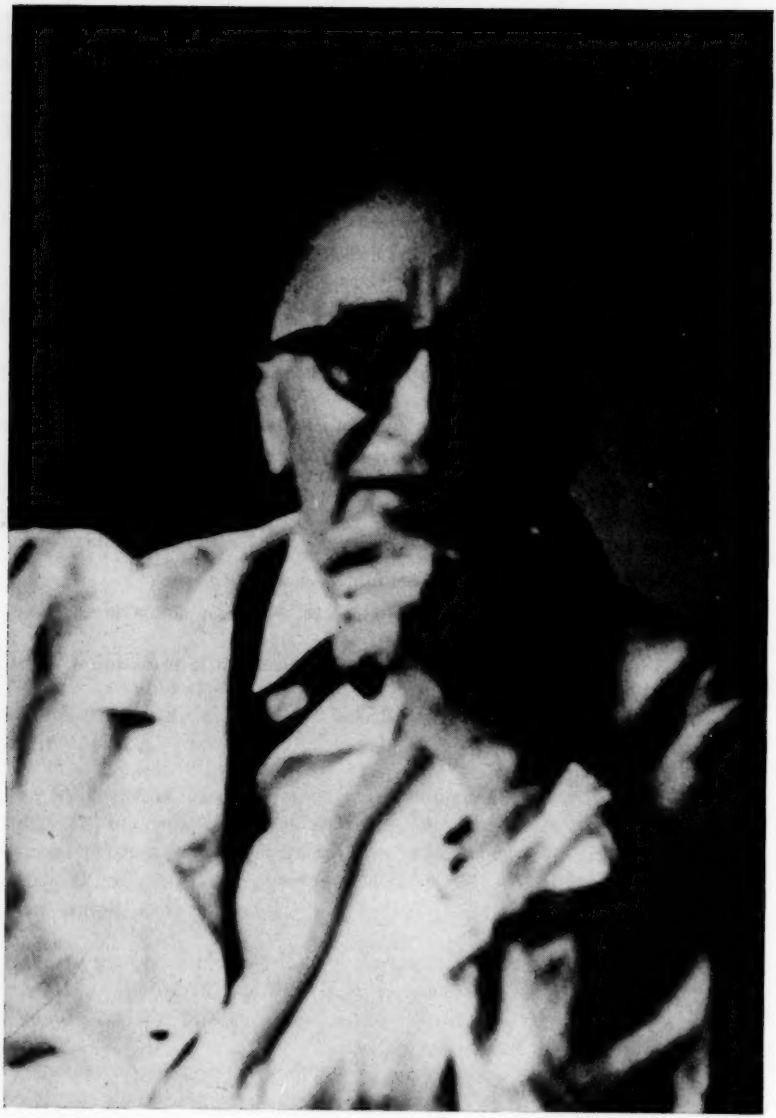

André-Thomas

Member of l'Académie de Médecine

NEUROLOGICAL EXAMINATION OF THE NEWBORN AND OLDER INFANT

RAYMOND LAFONTAINE, M.D.*

INTRODUCTION

In the field of the neurological examination of the newborn and older infant one of the most interesting and important contributions has been made by André-Thomas. He has written many articles related to the neurological aspects of the normal and abnormal newborn and older infant. His method and a form incorporating his ideas have been used for some time in the Division of Neurology. In view of the interest shown by our colleagues a summary of the neurological examination as described by André-Thomas and others is presented. This article is limited to part of his book published in 1952 and to a monograph on the same subject published in 1955.[1,2]

During the first days of life the newborn shows spontaneous activity. However, he is also capable of other reactions which can only be brought about by stimulating him — reactions which are in some ways comparable to those found at a later age when the cerebral cortex exerts its influence and has become the primary site of control. The study of this solicited activity and reaction of the newborn and older infant has been one of the great contributions of André-Thomas.

In order to clarify the description of the examination itself, a few explanatory remarks about terms follow:

When referring to tonus three components are included, consistency, extensibility and passivity. Consistency is evaluated by palpation and the muscular undulations obtained by shaking the corresponding segment. Extensibility is the maximum lengthening of which a muscle is capable when it is stretched away from its points of insertion. Extensibility is related to the muscular elasticity and to the resistance offered by the ligaments of the joints. Passivity is inversely proportional to the reaction of the muscle to stretching and is evaluated by the degree of resistance offered to passive mobilization of the segment directly seized. Passivity can also be evaluated by the degree of amplitude communicated through rapid mobilization of the above or subjacent segment. There is no idiomuscular reflex to percussion in the newborn.

Spontaneous motility connotes the absence of any actually avoidable interference. However, it is probable that besides the imperceptible exteroceptive afferences, some proprioceptive and interoceptive afferences constantly exist. Therefore, the spontaneity includes (like reflectivity) some afferent paths, centers, internuncial relations and efferent paths.

Reactions are distinguished from reflexes by their greater complexity and their less constant appearance. This is exemplified by such influences as (a) satiety or hunger on the reaction of the cardinal labial points, (b) modalities of general tonus on the tonic flexor reflex of the digits or on the digital reactivity to a stimulus applied to the

*Division of Neurology and Psychiatry.

internal border of the little finger or of the palm of the hand, and (c) the inhibitory action of the cry.

EXAMINATION

NEO-NATAL PERIOD: NEWBORN

The newborn period as opposed to the infant or post-neonatal period corresponds approximately to the first ten days of life. During this conventionally defined period some important changes have already occurred due partly to the increasing remoteness of the obstetrical trauma and partly to the evolution of the central nervous system in its new enviroment.

General posture: In supine, in prone position, suspended with face down or up, and in vertical suspension, head down, the posture of the newborn reflects both the foetal posture and the state of tonus which are responsible for the posture. However, the head does not continue with the flexion but actually gives way to its own weight. It is dragged in the supine position and is always extended when the newborn is crying. The head tends to remain in contact with the level of the crib.

Passivity: The passive rotation of the vertically held body whether done rapidly or slowly does not bring about any reaction in the opposite direction. Changes in position of the body do not bring about reactions of the head or limbs, such as the labyrinthine or cervical reflexes described by Magnus. The head in passive rotation at this age does not appear to bring about any change in the posture of the limbs and swings freely in all directions when the body is shaken. However, when the head is seized and then moved in various directions the flexion encounters more resistance than the extension. By repetition of a postero-anterior push over the occiput, the tonus of the extensor muscles of the head and neck increases to such an extent that the body axis can be raised by the occiput, the head remaining in line with the trunk. This same reaction can be seen when the child is crying or sucking its thumb.

The contrast between the passivity of the head when the body is shaken (induced passivity) and the resistance offered to occipital and frontal taps is another manifestation in the spatial reflectivity of the importance of the chronological factor.

Spontaneous motility: During the cry, which usually occurs after the first respiration, we see the earliest manifestations of the tonicity of the head and neck. Spontaneous rotation of the head in supine and prone positions occur. The latter position allows the newborn to free his nose. A lateral inclination of the head is not usually seen at this age.

Reactions: The head is capable of reacting by some very discordant movements in response to even a slight stimulus applied to the face. By rubbing the ear lobe lightly or by tickling the nasal septum we obtain a rotation of the head towards the opposite side.

The reaction of the cardinal labial points is demonstrated by the sucking reflex which is the first post-natal act to manifest itself rhythmically. It may even precede the first respiration. On touching lightly the right labial commissure we obtain the lowering of the right half of the inferior lip, and the tongue will orient itself towards

the stimulus. If the finger is then taken further way while remaining in contact with the cheek, the head turns to seek it. If the medial part of the lower lip is stimulated that lip and the tongue drop. If the examining finger moves downward towards the chin the mandible is lowered and the head flexes. The reaction is elicited more easily before feeding than after. In some newborns any contact with the face elicits some of these reactions. A finger introduced between the lips is sucked at. If the finger is progressively withdrawn the head flexes pursuing the finger. This reaction is strong enough to overcome the effect of weight and certain contractures in opisthotonos (meningeal hemorrhage, kernicterus).

Conflict of reactions: The simultaneous excitation of the right labial commissure and of the right ear causes the inferior half of the right lip to lower and the tongue to move to the right, but the head to turn towards the left.

Ocular and visual reactions: Th eyes of the newborn open simultaneously or separately. They are attracted by daylight, close under strong light (dazzling reflex of Peiper), and the pupillary reflex to light is present at birth. During the first days of life when the head is passively turned, the eyes follow only after the head has stopped moving. The eyes then orient themselves and stare straight ahead. This is known as the doll's eye phenomenon. The reaction loses some of its regularity and constancy and gradually disappears about the end of the first ten days.

Auditory reactions: A sudden and loud noise may cause blinking of the eyes (cochleopalpebral reflex) and may or may not be accompanied by a generalized start. The reaction is exhausted by repetition of the stimulus.

Gustatory reactions: The introduction of a sugar-coated finger between the lips of the newborn results in a sucking reaction, licking of the lips and pursuit of the finger while it is withdrawn and grazing the cheek. With salt the sucking is less or nil, a wry face is seen, and the newborn will force the finger back with its tongue, making irregular movements with its head. These contrasting reactions are most marked soon after feeding. The newborn, although he cannot identify the nature of sugar, salt or quinine sulfate, answers with a different affective reaction which precedes knowledge of the quality and nature of the stimulus.

Reflexes: Percussion of the base of the nose causes blinking of both eyes known as the naso-palpebral reflex. Percussion of the superior orbital region causes blinking of the homolateral eyelid known as the MacCarthy reflex. The ciliary reflex is manifested by touching the eyelashes lightly causing the eyelids, especially the homolateral one, to blink. The corneal reflex is present. The mandibulalr reflex is more brisk during the inspiratory phase of the cry.

UPPER LIMBS

The general attitude and relations between the spontaneous attitude of the upper limbs and the cervico-cephalic segment is referred to later in the presentation. When the infant is vertically held with head down the usual flexor posture of the limbs is maintained.

In the upper limbs the extensibility is greater and resistance to stretching (passivity) weaker for the extensor muscles. The reverse is true for the flexor muscles in all segments.

When the body is shaken, movement of the upper limb is slight and a dangling of the hand results. Amplitude of motion of the upper limb also evalutes the passivity of this limb when it is thrown back and forth. If the upper limb is raised a few inches and then released (the infant being in supine position) the limb will not fall abruptly on the table. If the fore-arm is extended and then released it returns quickly into flexion. Correspondingly, if the hand is flexed and then released it will return quickly to extension.

The newborn is almost constantly in movement which is varied, non-adapted (save for thumb-sucking), non-symmetrical (except during the cry), not really athetoid and increased locally by any stimuli.

If the upper limb is passively extended along side the body while the infant is in prone position the head will turn, the fore-arm and the arm will flex and the frontal upper limb will tend to move forward. The same reaction is enhanced when the examiner applies pressure over the buttocks on the opposite side.

Reactions: Digital reactivity is manifested by tactile stimulation of the ulnar side of the palm or of the little finger. The little finger is extended, followed by extension successively of the fourth, third and the index fingers. The thumb is not easily moved. The fingers will then flex again but in the reverse way. This reaction requires a summation of stimuli and appears after a certain lapse of time. The proximal segments react only slightly in contrast to the reaction elicited in the lower limbs to an analogous stimulus. For this reaction it is best to examine the newborn in complete calm, soon after feeding. In the same manner localized movements of the hand and forearm can be induced, such as that of pronation by touching lightly the dorsal aspect of the hand.

Grasping* as a tonic reflex of the flexors of the digits will result if tactile stimulation with slight pressure is applied to the metacarpo-phalangeal furrow. All phalanges flex and the thumb flexes simultaneously. If an object held by the child is pulled, his grip is sufficiently strong to cause extension of the fore-arm and arm and finally his body can be partly lifted from the table.

Submitting the hand to a marked dorsal or palmar flexion increases the tonic flexor reflex of the digits in the first instance and decreases the reflex to disappearance in the second.

As later in active prehension the extensors of the hand and the flexors of the fingers contract synergically. When the first are deficient the tonic flexor reflex of the digits must be explored by passively raising the hand. The passive flexion of

*The word "grasping" should be used only when referring to the pathological phenomenon described under this name in adults. Its relations with the tonic flexor reflex of the digits as observed in the normal infant are far from being clearly established.

the hand enhances the extension of the fingers as a result of a light and repeated dorsal touch to the last phalanges. This stimulus is more efficient in a period of spontaneous agitation than in a period of calm.

Reflexes: Tricipital reflex is not elicited because of the predominance of the flexor tonus in the fore-arms. If the other muscles are involved in paralysis while the triceps is intact, this reflex will be present. Palmo-mental reflex appears to be absent in the newborn.

In conformance with the opinion of Magnus the position of the upper limbs in the normal newborn does not seem to be related to the spontaneous or passive rotation of the head. The newborn sucking his thumb flexes the frontal fore-arm, that is, the arm toward which the head is turned, to an equal extent or even more so than the occipital fore-arm, the arm away from which the head is turned. The return into flexion of the previously extended fore-arms which are then released is done at an equal speed and amplitude on both sides, regardless of the side on which the newborn rests.

The "arms of the cross" reflex is induced by any brisk or rapid maneuver which will mobilize the head in relation to the body axis. It may be induced by the participation of the cervico-cephalic muscles to a generalized start, as in the test described by Moro.

Spontaneous appearance of the "arms of the cross" reflex occurs when the newborn is held in the sitting position, the head first flexed and the upper limbs in their usual position. After a few seconds the head erects, moves beyond the prolongation of the vertical axis and falls back under the influence of its own weight into the hand of the examiner. The arms are abducted, the fore-arms, the hands and fingers extended. However, when the head is passively broughts back into flexion the upper limbs recover their position in flexion. When this second part of the reflex is spontaneous, it is called the embracing reflex.

The Moro reflex may also be induced by raising slightly, but briskly, the child seized by the thighs in dorsal decubitus, the head remaining in contact with the table. The maneuver, which consists in mobilizing the head of the newborn by allowing him to fall back on the table after he has been raised by the hands a few inches, has the advantage of moving his body less but the disadvantage of interferring with the upper limb which is an effector segment and must participate at the beginning of the reaction. The Moro reflex is inhibited homolaterally or bilaterally by the tonic flexor reflex of the fingers. An object held tightly in one or both hands is not dropped.

TRUNK

Flexion of the trunk progresses at a greater rate than does extension. When the trunk is swung in the antero-posterior direction the dangling is more marked at the level of the lumbo-sacral articulation than in the lower limbs. Spontaneous movements of flexion, extension, rotation and lateral inclination are not found at this stage.

Repeated pricking of the skin of the back from the twelfth rib to the iliac crest

causes curving-in of the trunk on the stimulated side with folding of the skin. The curving-in reflex is one of the most constant in the normal newborn as is the Moro reflex. The cutaneo-abdominal reflex, the cremasteric reflex and the anal reflex are generally not observed at this age.

LOWER LIMBS

The extensibility is greater and the resistance to stretching (passivity) less for the extensor muscles than for the flexor muscles in every segment. Dangling of the lower limb is slight when the body is shaken. The passivity is reduced for all segments, even for the feet. Dangling of the feet is less easily obtained than of the hands.

Spontaneous motility is demonstrated by alternate movements of flexion and extension, by volleys, in decubitus dorsalis and ventralis. There is also a contrast between the relative inactivity of the upper limbs and the lower limbs in this last position. This rhythmical activity is probably related to the automatic walk (see further).

By pricking one of the inguinal folds contralateral adduction of the thighs results. To produce the tonic flexor reflex of the toes tactile stimulus is applied to the metatarsophalangeal furrow using the shaft of a pin. Flexion of the toes occurs, and they are capable of holding an object. The reaction can also be induced by pressure applied to the anterior heel at the distal extremity of the first interosseous space. Its intensity is increased or decreased when the foot is passively brought into dorsal flexion or plantar flexion respectively.

Crossed extension is produced by stroking along the planter aspect of one foot while the limb is retained in extension. Flexion follows, then extension and adduction of the opposite lower limb with extension and fanning of the toes.

By pricking the plantar aspect of the foot extension of the toes, dorsal flexion of the foot and flexion of the leg and thigh result. No repetition of this stimulus is necessary. The reaction is rapid, almost immediate (see reaction of the upper limb to an analogous stimulus).

The tactile excitation of the plantar aspect of the great toe may give rise to the isolated extension of this toe. However, tactile excitation of the lateral aspect of the foot rarely produces the isolated extension — slow and steady — of the big toe as described by Babinski in the involvement of the pyramidal tracts in the adult. Flexion and extension are obtained with fanning of all toes, and at times, flexion on one side and extension on the other when the stimulus is applied simutaneously over both soles. The spontaneous movements may interfere with the interpretation, and these reactions must be looked for during a period of calm.

The patellar reflex is brisk and of slight amplitude with extreme, frequent, almost constant contralateral reflex of the adductors. The Achilles tendon reflex does not exist normally because of the relaxation of the gastrocnemius and soleus muscles and because of the relative hypertonia of the dorsal flexors of the foot. When dorsal flexors of the foot are paralyzed while the gastrocnemius remains intact the Achilles reflex is elicited.

On percussion of the heel there is brief extension and movement of the lower limb followed by an abrupt flexor movement of more amplitude.

STRAIGHTENING REACTIONS — LOCOMOTION

When the newborn is held vertically and the plantar soles are placed on the floor there is straightening of the feet and different segments of the lower limbs which may be obtained on one leg only. Standing is solid but should be tested for each leg separately. Standing is not constant at first and is, at times, facilitated by passive extension of the head.

For vertical straightening, the newborn is held in the examiner's arms facing forward. The trunk and the head are flexed under the influence of their weight.

With one hand pressure is applied to the soles of the feet and the ankles are manipulated. This maneuver elicits straightening of the different segments of the body. If the face or the nape is tickled the head and trunk straighten.

The primary or automatic walk is elicited when the newborn is held in a vertical position with feet on the ground and lightly propelled. At first he lacks equilibrium. Coordination is good and rhythm regular. The heel is laid first with a strong dorsal flexion of the foot. Associated movements of the upper limbs are not present. The newborn cannot walk backward. Within a few days the walking movements become more pronounced and the dorsal flexion of the foot less evident.

POST-NEONATAL PERIOD — MIDDLE AND LATE INFANT

The neonatal period is considered to be the first ten days of life. The remainder of the first year of life and that period immediately following when the principal functions of the adult type make their appearance is known as the post-neonatal stage. During this period the cephalic perimeter increases considerably paralleling the increase in weight of the brain. Some marked changes in behavior are also noted, indicating the passage from predominantly subcortical activities to controlled activities by superior centers, but at varying degrees. The primary reactions are modified or disappear and are progressively replaced by different reactional modalities. In a few instances, the control of a primary activity by the superior centers is first manifested by an inhibition. Such phenomenon is apparently the case when considering the static and locomotor aptitude of the lower limbs.

The clinical investigation at this stage no longer proceeds by regions as in the newborn but is oriented towards investigating the evolution of functions, their modifications and progression towards a final pattern.

EVOLUTION OF THE TONUS

The extensibility and passivity of the flexor muscles increase progressively in the four limbs. At the beginning of the second trimester the flexor tonus at rest evidently decreases in the different segments of the upper limbs including the fingers. The extensor attitude of the lower limbs, however, occurs at a later date. During the second month, the evolution of the tonus is more rapid and at the cervico-cephalic level, but in this instance it is toward an increase of the flexor tonus. These modifica-

tions in tonus result in parallel changes in posture. The tonic neck reflex may be positive in one infant or newborn and negative in another.

OUTCOME OF THE PRIMARY REACTIONS

The cardinal labial points reaction may persist for many months, but it is submitted to some modification by the cortex. The strength and amplitude of the Moro reflex decrease rapidly, probably in relation to the modifications of the tonus in the upper limbs and to the progressive fixation of the head. About the age of one or two months an incomplete Moro reflex can be demonstrated by raising the body axis briskly. The arms then are abducted to a certain degree and the fingers are not completely extended. The curving-in reflex of the trunk becomes weaker and disappears during the second month to reappear much later. Crossed extension reflex disappears in the lower limbs usually before the end of the first month. At this stage the opposite inferior limb flexes and remains in this position. Later, about the third month, the crossed extension reflex reappears but with some cortical characteristics (see discussion of tonic flexor reflex of the fingers and the primary stance and walk).

At the age of approximately three to seven months the Landau reflex can be elicited spontaneously. With passive flexion of the head the lower limbs are flexed and with passive extension of the head the lower limbs are extended.

NEW REACTIONS

Visual: The doll's eye phenomenon disappears a few days after birth, but the dazzling reflex persists. During the first ten days orientation of the head and eyes to a subdued light may be seen; however, it is not restricted to this period. There is intermittent fixation of the infant's gaze at about one month of age.

Visual pursuit of an object appears at the age of two weeks. An infant will follow intermittently and for a short distance an object held close and horizontally. About three or four weeks of age the head participates in the visual pursuit and must be held in order to appreciate the amplitude of the movements of the eye. At three months a posture facilitating the flexion-extension of the head makes possible the visual pursuit of an object held vertically. Convergence, accommodation, and visual-somatic associations (see prehension) appear at this time. The blink-reflex to threat is of a later date.

Audition: In general the orientation of acoustic origin appears later than that of visual origin. During the first month a small bell rung close to the infant may provoke the cochleo-palpebral reaction, a start or modification of the respiratory rhythm, or of general activity. A few weeks later the infant may lie still at the sound of a familiar voice such as that of his mother, or respond to it by looking toward the speaker. Only later will he turn his head towards the sound of a falling object.

Tactile Afferences and Painful Afferences: In the newborn, pinching the big toe provokes a generalized reaction, scream or wry face. In addition to this reaction we must study (a) the withdrawal of the stimulated segment and (b) the placing of the child's hand on a stimulated area. At four or five months the child is able to remove a handkerchief covering his face. As early as the tenth month and certainly

by the end of the first year he will bring his hand to the homolateral region which has been pricked lightly, or even to the contralateral temple if the corresponding hand is restrained.

STANCE AND EQUILIBRIUM A: As Related To The Straightening Pattern From Prone:

About the end of the first month the newborn raises his head slightly, but it falls back immediately. Progressively, the head tends to fix itself in the raised position. Fixation of the head is more definite about the third month, and the infant is also able to raise the upper part of the trunk with the help of his upper limbs. This extension progresses from the nape to the lumbo-sacral region and is facilitated by the development of the upward gaze.

Displacement of the upper limb forward may be seen earlier when facilitated by a tactile stimulus which is applied to the hand after the upper limb has been previously extended along the body (see newborn). Later the displacement may be modified by affectivity; for instance, the infant's extending the arm towards a familiar object or towards his mother. About the third month there is support upon the fore-arm facilitating the elevation of the thorax and head. A few weeks later the fore-arms may be extended on the arms, the support being first taken on the dorsal surface of the flexed fingers then on the palm of the hands.

About the sixth or eighth month, if the child is grasped and thrust from above downwards and laterally the corresponding upper limbs move towards the floor in order to seek support (static aptitude of the upper limbs). The different segments extend before establishing contact with the table. At first, support is taken with the hand closed and later with the palmar face of the hands. Support is strong enough to sustain the weight of the body and must be evaluated for each limb separately. This reaction may be obtained even when the infant is blindfolded as previous visual associations are not necessary. Even at a more advanced stage the hand will not open if it is holding an object.

Placing Reaction of the Hand: When the examiner places the dorsal aspect of one of the infant's hands along the edge of the table there results flexion of the different segments of the upper limbs, bringing the hand over the table, and at the age of 3 or 4 months complete straightening of the upper limb. Support is first taken on the fore-arm, then wrist and later with the hand opened, and still later the fingers spread. Again the visual afferences are not necessary.

STANCE AND EQUILIBRIUM B: Sitting Position: During the first weeks of life, when the infant is pulled by the hands into a sitting position from the supine, the head falls back. About the age of three months the head is maintained in the prolongation of the body axis. The child, as yet, does not contribute to the movement. The lower limbs are often in flexion-abduction. Later he moves his head forward, the trunk flexes actively and the lower limbs are raised from the table.

Towards the end of the first six months the maneuver described above elicits a *spontaneous movement* strong enough to necessitate only a light pull. Later the child will sit alone. Gradually he will raise himself to a sitting position with the help of

his upper limbs from the prone position, the hands and knees position and later from the supine.

At the age of four or five months lateral falls are frequent. However, the infant will not fall laterally when placed in a sitting position, his back resting against a pillow. If the trunk is not held it will fall forward. Early in this stage the infant will not reach with his hands for support as he does at five months. The gradual straightening of the trunk which has been passively flexed results in backward falls at the beginning.

At about six or seven months the infant will remain in a sitting position without support but will not resist even a slight thrust. Resistance of the trunk towards a lateral thrust is developed earlier than towards a backward thrust. In the lateral thrust the child will fall over, making no attempt to prevent the fall with his hands. (reflex d'arcboutement of the upper limbs or parachutism). However, at eight months the contralateral arm is abducted, the fore-arm extends on the arm, the fingers open before contact, and the support is obtained laterally on the palm of the hand and fingers.

At ten to twelve months if the child is pushed backward the upper limbs are thrown back. The hands are generally oriented from behind forward as a result of a slight degree of internal rotation of the arm and pronation of the fore-arm. In these two reactions of "arc-boutement" the support is first taken with the hand closed. Even at a later stage the hand is not opened when it is already flexed over an object.

STANCE AND EQUILIBRIUM C: Upright Position: The ability of the newborn to straighten when the feet are placed on the table and to maintain an upright posture disappears progressively. About the age of two months the feet are not well oriented, the support is taken on the toes and later on the dorsal aspect of the flexed toes (digitigrade attitude).

About the fifteenth day when the infant is placed with the dorsal aspect of his foot along the edge of the table the first stage of the placing reaction is seen. Flexion of the different segments of the lower limbs brings the foot over the table. The second stage consists in straightening after active or passive application of the sole of the foot on the table and the reaction is only elicited later.

The straightening reaction is lost when the feet are placed on the floor (physiological astasia). Instead we obtain a passive flexion of the trunk on the thighs and persistence of the digitigrade attitude of the feet while the child is held. The stage lasts approximately until the end of the first six months but may vary. Towards the end of the astasic stage there is flexion alternating with extension in the lower limbs and trunk (leaper's or jumper's stage).

As maintenance of the upright position becomes progressively more durable and solid the support is taken on the plantar sole of the foot with the toes extended (definitive upright position). Each limb must be evaluated separately. About the ninth or tenth month the infant is able to stand with support.

STRAIGHTENING AND EQUILIBRIUM D: When Vertically Suspended: Straightening persists in the infant for some time and is brought about by the same maneuver as in the newborn. However, before the end of the first six months the straightening becomes spontaneous.

Equilibrium is demonstrated at the cephalic level by supporting the infant's head which is inclined laterally. Resistance offered by the head rapidly strengthens. After a few weeks, and even during the first days, there exists a real nystagmus of the head in this position. The head becomes totally fixed at about three months of age. Only at the beginning of the second six months does resistance of the trunk to slow anterior and lateral inclinations appear and increases progressively during the following months. Resistance of the head and trunk to brisk inclinations appears only later, the trunk then moving to the opposite side.

LOCOMOTION: The *first walk* of the newborn persists for a few weeks but may vary. Progressively, contact with the floor is made with the tip of the foot. Rapidity, regularity of rhythm and coordination diminish. Each foot is lifted less quickly from the floor. Between two and six months the feet drag when the infant is propelled (physiological abasia). Towards the end of this period the infant has a tendency to leap, jump or beat the floor first with one foot and then the other. A few weeks later steps may again be produced by lifting and propelling the child (*final walk*). At the beginning of this stage there is neither rhythm nor coordination. The movements are jerky, at times isolated, and the flexion is marked at the level of the knees and hips. Contact of the foot at first is digitigrade, becoming plantigrade and then with the heel.

At this stage the child in order to maintain equilibrium when walking supports himself by holding on to furniture or someone's hand. At the beginning of the spontaneous walk the upper limbs are held in strong abduction. All segments including the fingers are extended and the feet thrown apart. Slowly the base of sustentation and the abduction of the arms diminish, and the associated movements of the upper limbs begin to manifest themselves.

As was seen before, the upper limbs appear to act quite independently of each other in the newborn. While crossed reflexes were noted as being numerous in the lower limbs of the newborn none are known to exist at that stage in the upper limbs. An painful stimulus applied to one of the upper limbs may bring out a generalized reaction, but no special correlation between both upper limbs were noted.

During the physiological abasic period of the lower limbs each upper limb begins to show a tendency to rhythmical progression. This tendency can be seen before the stage of spontaneous walk when from a position on hands and knees the child is lifted by the trunk and lower limbs and propelled on the floor (wheelbarrow maneuver). At first the infant advances on his fore-arms with hands closed and later on the extended upper limbs supporting himself with the palm of his hands. In contrast to the lower limbs, the alternate movements in the upper limbs gradually improve as soon as they appear and are never lost.

The same observations can be made for the static aptitude of the upper limbs. The sight or call of the mother helps to bring out these alternate movements of the upper limbs, and the infant progresses correctly on his hands while he is not yet able to walk.

PREHENSION AND GRASPING

Prehension is a cortical phenomenon both purposeful and voluntary. The phenomenon consists of the opening of the hand followed immediately by its closure when the infant sees, comes in contact with or hears the sound of an object. In the newborn the object once grasped is held, released or manipulated without apparent purpose. At this time the grasping reflex seems to consist more of tonic reflex of the flexors of the fingers. The prehension *per se* becomes possible because of the decrease in the permanent flexor tonus of the upper limbs and of the tonic flexor reflex of the fingers.

Sight, which limits the improvement or perfecting of tactile sense is of primary importance in the approach and in reaching for an object. With renewal of visuo-motor association and progress in visual memory the infant becomes capable, upon seeing an object, of reaching for it without continuing to look at it.

About the age of three months the sight is concentrated on the hand. In this way the associations between the visual and somatic afferences are established. Auto-exploration is, however, not only visual. The fingers of both hands come in contact with each other. Later they will discover the knees and feet.

Affectivity and environment also enter into the development of prehension, spontaneous reactivity. During the examination, for instance, behavior of the infant is seen to vary according to his familiarity with the person presenting the object. The characteristics of prehension and tonic flexor reflex of the fingers can best be differentiated by noting the isolated or separate mobilization of the fingers on the object and manipulation of the object after the opening of the hand.

Later when the infant brings an object grasped by chance to his mouth, he demonstrates a combination of the tonic flexor reflex of the hand and the thumb sucking reflex. At the sight of an object the child first shows generalized restlessness and beating of the arms soon combined with movements of opening and closure of the fingers which are kept at a distance. Later these movements are combined with those of approach and finally pursuit of the object. The approach is first bilateral then unilateral (mirror-like) before the laterality becomes established.

Mobilization first predominates at the level of the shoulder (abduction-adduction, then flexion and extension). Movements of the elbow are well developed by the end of the first six months of life and are slowly coordinated with movements of the other segments. Motility of the wrist (flexion, extension and ulnar inclination) increases rapidly during the second six months while at the same time the bidigital "claw" of the thumb and index finger appears. Lateral inclination of the wrist facilitates reaching for the object with the thumb and index finger and the moved hand is away from the visual field. This movement is facilitated by the predominance of the ulnar extensibility

of the hand, a disposition frequently encountered and thought to be congenital. The preliminary opening of the fingers is, at first, hypermetrical. At the end of the first year it becomes related to the dimension of the object.

The participation of the trunk in prehension increases rapidly once the sitting position is mastered (flexion-extension, then torsion, the shoulders brought forward). At this stage the fields of prehension and sight develop parallely. Prehension facilitates the rotatory movements of the trunk. Early in this stage the object is held in the tip of the palm of the hand and all phalanges are flexed.

The development of prehension is characterized by the substitution of the middle and distal phalanges to the proximal phalanges, by a more active part from the radial fingers and finally by isolated movements of the proximal phalanges and the opposition of the thumb to the index and other fingers. Slowly the infant adapts his strength to the weight and physical qualities of the object.

Around the beginning of the second six months manipulation associated with movements of the arm, fore-arm and hand in an attempt to bring the object into the visual field becomes evident. It is first bilateral like the approach.

CONCLUSION

Throughout the examination of the newborn from the time of birth to the stage when the principal functions of the adult type are established we see reaction patterns change continuously. Parallel progression or regression of reflexes, tonus and motility become evident as the child grows and is affected by environment.

It appears that continuous experience prepares the cerebral cortex for an accumulation of afferences and appearance of new reflexes. The cortex seems to act as a register while undergoing constant transformation, multiplying these accumulations in a chronological and spatial order, associating and classifying them through phases of trials and renewals. At the same time the motility is increased and extended and conductibility improved. The cerebral cortex accumulates new afferences which are integrated in the sensations and later in the perceptions. However, many, from the anatomical and functional point of view, although picked up by the cortex, remain below the level of consciousness.

Many tests described above are not easily performed. All newborns are not equally tolerant to stimuli and by nature are labile. The rapidity of response to stimulus, its briskness and persistance are equally variable. When a stimulus is repeated it is not uncommon to see the reaction less marked the second time, still less the third and finally disappear. Extinction of many vegetative or affective type of reactions upon repetition of the stimulus is not rare.

Particular attention, however, should be given the main vegetative functions, general state of tonus, Moro reflex, curving-in reflex of the trunk, contra-lateral adductor reaction of the thighs which are most constant in the normal newborn. Any asymmetry of tonus, motility, rapidity of degree, regularity, osteo-dendinous and cutaneous reflectivity must be considered as abnormal either on a constitutional or

pathological basis. The prolongation of the least activity of a limb over a certain period must be given a similar interpretation. Asymmetry appears to indicate a morbid state more clearly than does a more or less marked motor, tonic or reflex activity which is strongly bilateral and symmetrical unless definitely abnormal.

On the other hand, although all signs are not equally important, every phenomenon of provoked motility may help to inform us on the state of anatomical and functional arcs which are unexplorable at this age through examination of the senses or of movements executed on command, as seen at a more advanced age. Besides the physiological interest of studying behavior of the newborn and older infant, the proposed neurological tests have a greater value when we consider that they allow us to detect an anomaly, an asymmetrical activity, some reactions and to uncover within the first few months of life a pathological process whether constitutional or acquired.

The newborn and older infant are exposed to factors of various degrees of morbidity and to more or less destructive lesions of the cortex. Whether these morbid factors date back to the time of birth or soon after, such as the third or sixth month of life, they will not manifest themselves under the same semiological aspect. Different impairments of function will appear according to the stage of anatomical development and physiological maturity that have been attained at the time of aggression.

In contrast with normal semiology, the pathological will vary with the stage of development. Besides the systematic affections and asymmetries an abnormal state may be due to the persistence of a behavior which should have disappeared and/or to a delay in acquiring the new pattern.

The utmost caution is necessary when referring to the interpretation to be attributed to the time of appearance or dissappearance of any behavior modality. Here, as in psychology, the accepted period of appearance of a phenomenon is quite extensive. The neurological curriculum is a series of linked reactions, a sort of sketch or pattern already prepared by the anatomy or the histology. We do not necessarily find the same order of innovation and progression from one infant to the next. Even if both appear normal, a few links in the chain of events and reactions can be displaced or interchanged. Therefore, we must only refer to the dates or ages given previously as points of reference, as an approximate index of function.

The experience teaches us to be extraordinarily cautious when speaking of prognosis, particularly when the critical stage — evidence of maturation of the cerebral cortex — has not yet been passed. At this period some previously existing abnormalities of the cortex, until then latent, may begin to manifest themselves in an infant previously considered normal. Conversely, some substitution may be established which may mitigate the previous pathological manifestations or cause them to disappear entirely.

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INTRODUCTION TO NEW STAFF PERSONNEL

ARTHUR B. EISENBREY, M.D. joined the Neurological Surgery staff July 1, 1957. Originally from Cleveland, he received his M.D. degree from Western Reserve University in 1948. Training in neurological surgery was completed at the University Hospitals, State University of Iowa.

WILLIAM K. ELWOOD, D.D.S. joined the Dental staff as Research Associate July 1, 1957. He is a native of Ohio and 29 years of age. He received a B.A. degree from Ohio Wesleyan University, 1950, M.S. degree in anatomy from Ohio State University, 1953 and from the same school a D.D.S. degree in 1957. Dr. Elwood is married and resides at 8583 Manor.

HAROLD M. FROST, M.D. joined the Orthopedic staff September 1957. A native of Boston he is 36 years old. After attending Dartmouth College he received the M.D. degree from Northwestern Medical School in 1945. He interned at Mary Hitchcock Memorial Hospital, Hanover, New York in 1946. A surgical residency and first year residency in orthopedic surgery were completed at Worcester City Hospital, Worcester, Massachusetts, 1949-1950. His orthopedic training was completed at Buffalo General Hospital in 1952. Dr. Frost served as attending orthopedic surgeon, Buffalo General Hospital and Buffalo Children's Hospital, 1952-1953. From 1953-1955 he was attending orthopedic surgeon, Grace Hospital, Mercy Hospital and junior clinical assistant in orthopedic surgery, Buffalo General Hospital. From 1955 until the present he was Assistant Professor of Orthopedic Surgery, Yale Medical School. Dr. Frost is a diplomate of the American Board of Orthopedic Surgery. He served with the Medical Corps United States Naval Reserve from 1946-1948.

MICHAEL A. GRISHKOFF, M.D. joined the staff of Medical Clinic No. 1 as Assistant Physician June 20, 1957. He is a native of Yugoslavia and 35 years of age. In June 1949 he received his M.D. degree from Ludwig Maximilian University, Munich, Germany. An internship and residency training were completed at Henry Ford Hospital, 1950-1955. He was granted the M.S. degree in surgery from the University of Michigan. Dr. Grishkoff is a member of the Wayne County Medical Society, American Medical Association, Michigan Heart Association and American Heart Association. He served as Captain in the United States Army Medical Corps, Ireland Army Hospital, Fort Knox, Kentucky from June 1955 to June 1957. Dr. Grishkoff is married, has one child and resides at 17995 Birwood, Birmingham.

WILLIAM H. ISHAM, M.D. joined the Allergy staff as Associate Physician July 1, 1957. Dr. Isham is a native of Cleveland and attended the University of Chicago under the United States Army ASTP program from 1943 to 1944. Under the same program he attended the University of North Dakota School of Medicine and later Temple University School of Medicine where he received an M.D. degree in 1948. Dr. Isham interned at St. Anthony de Padua Hospital, Chicago from July 1948 to June 1949. Residency training under the auspices of the United States Army was completed at Tripler Army Hospital, Honolulu from September 1949 to December

1952. While with the Army Medical Corps he served as internist at the United States Army Hospital, Camp Gordon, Georgia. Later, and until August 1955, he served as Chief of the Medical Service at the same hospital. Prior to his present appointment Dr. Isham served as Assistant Chief, Medical Service, 98th General Hospital in Germany. Dr. Isham is certified by the American Board of Internal Medicine. He is married, has two children and resides at 14360 Freeland.

GEORGE EARL LaCROIX, M.D. joined the Gynecology-Obstetrics staff September 1957. He is a native of Massachusetts and 33 years of age. In 1948 he received his M.D. degree from Cornell University Medical School. Residency training included six months in pathology at Peter Bent Brigham Hospital, Boston, one year in general surgery at Malden Hospital, Malden, Massachusetts, and three years in gynecology and obstetrics at the Boston Lying-In Hospital, Free Hospital for Women. Prior to his present appointment Dr. LaCroix spent two years in private practice in Boston. He is married and has two children.

LEE BURDETTE STEVENSON, M.D. joined the Gynecology-Obstetrics staff September 1957. He is 33 years old and a native of Urbana, Illinois. After graduation from the University of Illinois College of Medicine in 1946, he served as Flight Surgeon with the United States Air Force for two years. He interned and completed a one-year residency at Pontiac General Hospital. For the following two and one-half years he completed residencies in gynecology and obstetrics and in pathology at St. Luke's Hospital, Chicago. Dr. Stevenson served on the teaching staff of the University of Wisconsin School of Medicine and was associated with the Jackson Clinic in Madison. He is married and has two children.

ELLIS J. VAN SLYCK, M.D. joined the Hematology staff September 1, 1957. A native of Philadelphia he is 33 years of age. He received his M.D. degree from Yale University School of Medicine in 1947. He served an internship at St. Luke's Hospital, New York City and completed residency training in internal medicine at the Veterans Administration Hospital, Newington, Connecticut, 1951. Following military service he was associated with the Alexander Blaine Hospital, Detroit for three years. He is married, has three children and resides at 353 Mt. Vernon, Grosse Pointe Farms.

THE HENRY FORD HOSPITAL MEDICAL SOCIETY

PROGRAM FOR 1957-1958

October 8, 1957 — Tuesday, 8:15 p.m. — Henry Ford Hospital Auditorium

The Edsel B. Ford Lecture

Molecular Genetics

Dr. George Gamow, Profesor of Physics, University of Colorado

November 19, 1957 — Tuesday, 8:15 p.m. — Henry Ford Hospital Auditorium

Collagen Diseases

Walter Bauer, M.D., Jackson Professor of Medicine, Harvard Medical School

February 11, 1958 — Tuesday, 8:15 p.m. — Henry Ford Hospital Auditorium

Carcinoma of The Thyroid

Rulon W. Rawson, M.D., Professor of Medicine, Sloan-Kettering Division, Cornell University Medical College

April 8, 1958 — Tuesday, 8:15 p.m. — Henry Ford Hospital Auditorium

Pruritus or Allied Cutaneous Sensations

Walter B. Shelley, M.D., Professor of Dermatology, University of Pennsylvania

May 13, 1958 — Tuesday, 8:15 p.m. — Henry Ford Hospital Auditorium

The Roy D. McClure Memorial Lecture

The Philosophy of Surgery

Harvey B. Stone, M.D., Professor of Surgery, Johns Hopkins University School of Medicine

ABSTRACTS OF RECENT PUBLICATIONS OF THE PROFESSIONAL STAFF OF THE HENRY FORD HOSPITAL AND THE EDSEL B. FORD INSTITUTE FOR MEDICAL RESEARCH

SCOPOLAMINE AS A PREOPERATIVE SEDATIVE IN CHILDREN. A. A. ANTONI AND F. A. HENNEY. J. Oral Surg. 15:192, 1957.

Scopolamine has proven to be superior to atropine, methantheline bromide, and various other drugs as a medication to ease apprehension, to dull awareness of the clinical surroundings, to reduce salivary and mucous flow, and to facilitate the administration of anesthesia for the extraction of children's teeth. Scopolamine has in addition, the advantage of producing a peculiar light amnesic action including the induction of anesthesia.

Tablets of 1/150 grain and 1/200 grain sizes are used. They may be administered orally either by the parent one half hour prior to an appointment or by the staff upon arrival of the patient at the office. Two and three year old children are given one half of one 1/200 grain tablet; four, five and six year old children receive one 1/200 grain tablet; older children take the adult dose of 1/150 grain.

No deleterious effects of great importance have been noted, although some children develop a transient rash and dilatation of the pupils for up to four hours. Although the cases studied received general anesthesia, it is recommended that its efficacy be studied when used for routine pedodontic procedures under local anesthesia.

CLINICAL EVALUATION OF CHLORPROMAZINE IN GENERAL ANESTHESIA FOR MINOR ORAL SURGERY. O. L. BALDRIDGE. J. Oral Surg. 15:199, 1957.

In a study based on 155 cases of minor oral surgery at Henry Ford Hospital chlorpromazine was found to be an excellent pre-anesthetic agent. It reduces a patient's apprehension without compromising his ability to respond and cooperate. With chlorpromazine, smaller dosages both of anesthetic and pre-anesthetic medications were required and induction was noticeably smooth and rapid; there was less post-operative vomiting.

For pre-operative sedation, 25 mg. of chlorpromazine may be given intramuscularly

to adults and 10 mg. orally to children about 30 to 45 minutes pre-operatively. The tachycardia and hypotension reported elsewhere in the literature in this drug have arisen from daily doses of 100 mg. maintained for a week or more; these complications did not appear in this series. Chlorpromazine has not yet, however, been evaluated for dental operations in patients in a sitting position, as opposed to the supine position on an operating table.

CAUSE OF DEATH IN RUPUTURED INTRACRANIAL ANEURYSMS. J. BEBIN AND R. D. CURRIER. A.M.A. Arch. Int. Med. 99:771, 1957.

This study of the consequences of the rupture of intracranial aneurysms covers a twenty-one year period during which time a tentative diagnosis of intracranial aneurysm was made in 243 patients out of 713 admitted to the University of Michigan Hospital with a diagnosis of subarachnoid hemorrhage.

Fifty-nine post-mortem examinations were done. In 35 cases death was thought to be due primarily to rupture of an intracranial aneurysm. Of the other 24 cases, no aneurysm was found in 8, 6 died from causes other than rupture of an aneurysm, 5 were considered to be definitely post-operative deaths, 4 died as a result of cerebral infarction in association with the aneurysm, and one patient died from pneumonia alone. Of the 35 cases in which death was thought to be due primarily to rupture of the intracranial aneurysm, intracerebral hemorrhage was found in 1, subdural bleeding in 2, intraventricular hemorrhage in 6, a combination of intracerebral and intraventricular bleeding in 26. There was a close relationship between the amount of bleeding into areas other than the subarachnoid space and the length of survival after the onset of the last, or fatal, hemorrhage. Deaths from intracranial aneurysms are thought to be due to one or more of the following causes: hemorrhage, operations, ischemic infarction, pneumonia, or compression and obstruction by a ruptured aneurysm acting as a tumor mass. Deaths due to hemorrhages from rupture of an intracranial aneurysm result from hemorrhage into other areas of the brain in addition to the subarachnoid bleeding. The most common is intracerebral hemorrhage with or without intraventricular hemorrhage. None of these patients died of subarachnoid hemorrhage *per se.*

EXPERIENCE WITH URINARY BLADDER REGENERATION. A. W. BOHNE AND K. L. URWILLER. J. Urol. 77:725, 1957.

The many pitfalls associated with diversion of the upper urinary tract are well known. In an attempt to overcome some of these difficulties, experimental work on bladder regeneration was started in 1950. The animal used was the dog. By this experimental work, the remarkable ability of the bladder to regenerate was demonstrated.

Subsequently, seven human cases have had a subtotal or total cystectomy. Reasons for these operative procedures were: two cases for severe, chronic, intractable interstitial cystitis; four cases of diffuse carcinoma of the bladder; and one case for arrested urinary tract tuberculosis. These seven cases were reported. It was felt that regeneration of the urinary bladder does occur in humans, as in dogs.

A functioning reservoir develops provided intermittency of filling and emptying can be maintained after the mold is removed. The reconstructed organ contracts to the extent that functioning capacity is no longer maintained when continuous drainage is necessary.

The post-operative course for humans is long and many complications are prone to occur.

INTRARENAL ARTERIOVENOUS ANEURYSM: CASE REPORT. A. W. BOHNE AND G. L. HENDERSON. J. Urol. 77:725, 1957.

A case is reported of a 63 year old man who presented with signs and symptoms suggestive of right renal colic. Intravenous pyelograms showed delayed function in the right kidney, a calculus at the ureteropelvic junction, and a large calcified mass in the area of the right kidney.

Retrograde pyelograms showed this mass to bear a close relationship to the right kidney pelvis. An aortogram showed an enlarged, tortuous right renal artery with a saccular dilatation which formed the previously seen calcific mass.

Operation revealed an intrarenal arteriovenous aneurysm. This was removed and the patient did well post-operatively.

THE STEROID-INDUCED PEPTIC ULCER. B. E. BRUSH, M. A. BLOCK, T. GEOGHEGAN, D. W. ENSIGN, AND J. W. SIGLER. A.M.A. Arch. Surg. 74:675, 1957.

It is generally accepted that adrenal steroid therapy leads to a greater incidence of gastro-intestinal ulceration than occurs in a patient population not receiving such medication. Ulcers are usually gastric rather than duodenal, although the patients in this series had a 50% incidence of prior duodenal ulcers.

Most patients respond to rigid ulcer treatment; some, even when steroid therapy is continued. Surgical intervention has been necessary in 10% of our series for perforation, severe hemorrhage, when healing is not complete in four to six weeks, or when clinical features of malignancy occur. A three-quarter gastrectomy plus vagotomy has premitted resumption of steroid therapy. A need for steroids pre and post-operatively is highly likely to exist in patients who have been receiving steroid therapy because of adrenal insufficiency due to pituitary supression.

PANEL DISCUSSION ON RHEUMATIC DISEASES IN THE AGED. Moderator: D. C. ENSIGN, *Panelists:* C. V. HECK, E. F. ROSENBERG, D. RUML AND L. E. WARD. J. Am. Geriatric, Soc. 5:239, 1957.

This discussion, conducted at the annual meeting of the American Geriatrics Society in Chicago on May 4, 1956, considered osteoarthritis, rheumatoid arthritis and gout as they are manifested in patients of the older age groups. Simple measures for the control of symptoms in osteoarthritis, as well as special measures for particular areas of involvement, were reviewed. Distinction between radiologic and clinical diagnosis of hypertrophic arthritis was emphasized. The manifestations of rheumatoid arthritis, particularly in the older patient, and the importance of a comprehensive study as the basis for a sound therapeutic program were considered in some detail. Discussion of therapy centered upon the necessity of treating the patient, since it is still impossible to treat the disease, and upon the subtle dangers of the use of corticosteroids. Diagnosis and treatment of acute gouty arthritis were dealt with briefly. Roles of the internist, the physiatrist and the orthopedist in the management of the several major rheumatic diseases were briefly outlined.

THE USE OF CHICKEN ANTISERUM FOR DETERMINATION OF PLASMA PROTEIN COMPONENTS. I. THE ASSAY OF HUMAN SERUM ALBUMIN AND GAMMA GLOBULIN. M. GOODMAN, D. S. RAMSEY, W. L. SIMPSON, D. G. REMP, D. H. BASINSKI AND M. J. BRENNAN. J. Lab. and Clin. Med. 49:151, 1957.

Methods have been described for the estimation of human serum albumin and gamma globulin based on a precipitin reaction using chicken antiserum. The turbidity produced may be measured with either a nephelometer or a spectrophotometer. Chickens have been found to produce a higher titre antiserum than other animals. The results of this method were compared with those obtained by means of paper

electrophoresis. When appropriate antigens are available it should be possible to apply this method to the estimation of other plasma proteins.

BETA-PROPIOLACTONE IN STERILIZATION OF VACCINES, TISSUE GRAFTS AND PLASMA. F. W. HARTMAN AND G. A. LOGRIPPO. J.A.M.A. 164:258, 1957.

Beta-propiolactone is a superior sterilizing agent for biologicals because of its capacity to inactivate rapidly and irreversibly a wide variety of bacteria, fungi, and viruses. At the same time, it causes minimal alteration of proteins, preserving their antigenicity, non-antigenicity or non-toxicity, as the case may be. This compound, therefore, offers a method for production of improved vaccines and a valuable means of sterilizing blood plasma. It is completely hydrolyzed to relatively non-toxic end-products, hydracrylic and beta-chloropropionic acids. All of these characteristics plus its ability to penetrate tissues rapidly make it especially useful in preparation of safer and more homogeneous tissue grafts of arteries, bone and cartilage.

CARCINOMA COEXISTING WITH MANSON'S SCHISTOSOMIASIS. W. S. HAUBRICH AND R. M. WELLS. Am. J. Digest. Dis. (n.s.) 2:335, 1957.

The coexistence of intensive infestation by Schistosoma mansoni and adenocarcinoma of the rectum in a young native of Puerto Rico is described. No claim for causal relationship is made; nevertheless, it is suggested that the link between inflammation and neoplasia, if such a link exists, is in the nature of hyperplastic polypoid granulomas resulting from an undefined stimulus acting in a susceptible tissue.

THE CHALLENGE OF PANCREATITIS. W. S. HAUBRICH, Clin. Med. 4: 1957.

Clinical clues to the diagnosis of acute pancreatitis are presented together with pitfalls in the interpretation of serum pancreatic enzyme tests.

TREATMENT OF THE PAINFUL TEMPOROMANDIBULAR JOINT. F. A. HENNY. J. Oral Surg. 15:214, 1957.

Pain in the temporomandibular joint may arise from a multiplicity of causes, but tension states superimposed on some occlusal abnormality appear most commonly.

The treatment of these conditions involves the general supportive care of the patient, the elimination or control of tension factors, and the production of a normal

balanced occlusion. Supportive care includes voluntary limitation of motion, a soft diet, the application of dry heat, and the administration of salicylates in 10 grain doses four times daily. Tension factors may be combated with barbiturates, muscle relaxants, increased out-of-doors exercise, insertion of a bite plane, and in severe cases pychotherapy is useful. Occlusal equilibration is achieved by adequate restorations, the extraction of hopelessly malpositioned teeth and the reduction of premature contacts in occlusion. Temporary symptomatic relief can be often obtained by the injection of hydrocortisone into the joint. In stubbornly refractory cases a high condylcetomy leaving the meniscus, may finally be necessary. This has produced excellent results when all other measures failed.

INGUINAL SWELLING DURING PREGNANCY. C. P. HODGKINSON AND J. KROLL. Am. J. Obst. and Gynec. 73:966, 1957.

This report considers 8 patients, observed through 21 pregnancies, in whom an inguinal mass was observed during the period of gestation. The incidence of inguinal protrusions was 1 in 1,021 deliveries during the 10-year period considered.

Three expanding lesions of the inguinal canal observed during pregnancy are compared: incomplete inguinal hernia, fibromyoma of the round ligament, and dilated veins of the inguinal canal and round ligament. All three caused an inguinal swelling simulating an incomplete inguinal hernia.

The significant disparate observations were: (a) incomplete inguinal hernia may suddenly disappear about midpregnancy to reappear after delivery; (b) an inguinal swelling caused from dilated veins is present only during pregnancy and generally appears about midpregnancy; and (c) tumors of the round ligament are never completely reduced, and the precise outline of the border can usually be distinguished.

Treatment, except for tumors, should follow a course of watchful conservatism.

HUMAN MELANOCYTES IN TISSUE CULTURE. FUNAN HU; RENATO J. STARICCO, HERMAN PINKUS, AND ROBERT P. FOSNAUGH, J. Invest. Derm. 28:15, 1957.

Human melanocytes of normal skins and benign pigmented nevi were successfully grown in tissue culture. Three types of cells were observed in cultures of human skin,

epithelial cells, melanocytes and fibrocytes. Dendritic cells giving positive dopa reaction, containing argentaffine granules and presenting other characteristic morphological features and staining reactions were identified as melanocytes. These cells appeared to represent a distinct type.

In corresponding sites, white and pigmented skins have approximately equal numbers of melanocytes per unit area. The pigment cells found in the dark colored skins were larger and more branched than those in the explants of the light colored skins. The dopa positive cells cultured from benign pigmented nevi were found to be even larger than any melanocytes seen in normal skins. There appeared to be a direct relationship between pigment-producing capacity and cellular size and complexity.

EFFECT OF ORAL ANTICOAGULANT (MARCUMAR) ON PROTHROMBIN AND RELATED COMPONENTS IN BLOOD COAGULATION. S. A. JOHNSON, M. J. CALDWELL, E. M. PRIEST. Circulation Res. 7:252, 1957.

For some time it has been known that the oral anticoagulants of the coumarin type reduce plasma levels of Prothrombin and Autoprothrombin I (Factor VII, Stable factor) following administration. Recently a third component Autoprothrombin II (PTC, Christmas factor) has been found to be reduced by these drugs. Prothrombin and Autoprothrombin I, both effect the Quick one-stage prothrombin time which is the test used to follow the effect of the oral anticoagulants on the blood coagulation components. However, changes in the level of Autoprothrombin II do not alter the Quick one-stage so the laboratory test does not usually reflect changes in this activity. An anticoagulant, the effects of which would be easy to control, would be one which only altered factors measured in the routine laboratory test. Since Marcumar does not reduce plasma levels of Autoprothrombin II it appears to be such an anticoagulant.

POTENTIATION BY SQUALENE OF ADRENAL AND THYMIC RESPONSES TO CORTICOTROPIN. I. T. KLINE, Endocrinology. 61:85, 1957.

Squalene, a 30-carbon triterpenoid, unsaturated, straight-chain hydrocarbon is a naturally occurring compound which can serve *in vivo* and *in vitro* as a precursor of cholesterol. In hypophysectomized rats, squalene, when injected subcutaneously for seven days (0.2 ml. dialy), augmented adrenal response to ACTH with respect to

both growth and cortical function, the latter having been measured by thymic involution. Simultaneous treatment with a squalene and ACTH resulted in 25% heavier adrenals and 50% smaller thymi than did treatment with ACTH alone, in doses which caused a 13-32% decrease in thymic weight. Squalene alone did not affect adrenal or thymic weights in hypophysectomized, adrenalectomized, or intact rats under the experimental conditions used. Neither mineral oil nor olive oil (used as control substances) augmented adrenal response to ACTH. Orally administered squalene did not potentiate response to ACTH, perhaps because of poor absorption from the intestine or because of hepatic utilization. These experimental data are consistent with the ideas that exogenous squalene can serve *in vivo* as a readily available, easily utilized precursor of glucocorticoids, presumably by way of cholesterol, that squalene augments ACTH action because the hydrocarbon enters the reaction sequence of adrenal corticoid biogenesis in such a way as to circumvent a rate-limiting step, and that squalene is a natural intermediate in steroid biosynthesis.

ORAL MANIFESTATIONS OF HEMATOLOGICAL DISORDERS. R. W. MONTO. J. Dent. Med. 12:47, 1957.

Diseases of the hematopoietic system are frequently exhibited in the oral cavity. Since the dentist is often the first to encounter disturbances in this area, it is essential that he be aware of the systemic importance of intra-oral lesions. The mucous membranes of the mouth manifest the early lesions and symptoms of primary hematologic disorders for various reasons. The vascularity of the mouth with the thin barrier of mucous membrane is easily broken by the continuous intra-oral trauma to produce bleeding phenomena in abnormal states. Many blood disturbances result in lowering of the number of leukocytes and inhibition of their normal function. This phenomenon together with the ever present bacterial flora of the oral cavity predisposes to infections and ulcerations.

*STEROID X-RAY DIFFRACTION POWDER DATA. J. PARSONS, W. T. BEHER AND G. D. BAKER. Anal. Chem. 29:762, 1957.

The fourth report in a series on this important subject is given for 32 additional compounds. In the full series data have been given for 138 steroids.

*Edsel B. Ford Institute for Medical Research.

SOME INTERESTING MIDDLE EAR PROBLEMS. H. F. SCHUKNECHT AND S. TRUPIANO. Laryngoscope 67:395, 1957.

The development of new surgical procedures has made it possible for present-day otologists to explore, describe and correct an increasing number of middle ear disorders. For example, we recently encountered an interesting problem consisting of a long-standing, surgically dislocated incus in a boy aged sixteen. Through a trans-tympanic approach to the middle ear the incus was replaced with excellent improvement in hearing. In the stapes mobilization operation otologists throughout the country have been utilizing more frequently the technique of using an automatic hammer on the rigid stapedial footplate. We have found that this results in an acoustic impulse of sufficient intensity to injure the organ of Corti in the basal turn and should, therefore, be used with caution. Another problem recently encountered during a stapes mobilization operation is round window otosclerosis. When the round window is blocked by a mass of otosclerotic bone it is, of course, impossible to expect improvement by stapes mobilization. For chronic bilateral middle ear and mastoid suppuration requiring surgery we have utilized a one-stage, bilateral operation in preference of two separate operations, providing the total operating time is not greater than four or five hours.

REPLACEMENT OF LONG AND NARROW ARTERIAL SEGMENTS. D. E. SZILAGYI, J. G. WHITCOMB, AND C. P. SHONNARD. A.M.A. Arch. Surg. 74:944, 1957.

A new arterial prosthesis made of Helanca nylon yarn is described which more nearly duplicates the characteristics of the human artery. It is woven, seamless, smooth-walled, soft, and easy to handle and has longitudinal elasticity. Among 23 implants, 7-10 mm. in diameter and 13-15 cm. in length, placed into the thoracoabdominal cavities of dogs as a proximal exclusion of the aorta, there were no failures. Gross and microscopic examination of 14 recovered implants showed excellent arteriogenesis of satisfactory tissue reactivity. Nine dogs with such implants are surviving in good health with angiographically normal prostheses after periods of observation up to 12 months. Although tensile-strength determinations on the implanted specimens reveal a significant and progressive decrease soon after implantation, this loss has not produced demonstrable gross changes in the prostheses. On the grounds of the satisfactory results of these animal experiments, during the past four months we have used the Helanca nylon prosthesis in 10 clinical cases of occlusive arterial disease. Two of these cases were instances of common iliac, and eight were those of femoral, occlusion.

One prosthesis, used as a femoral by-pass in a case of homograft failure, became thrombosed in the immediate postoperative period; the other nine implants have remained open both by clinical signs and by angiography during periods of observation of from two weeks to four months.

*CARBON REPLICATION OF PARTICULATES AND ULTRAMICROSCOPIC CRYSTALS. J. H. L. WATSON. Anal. Chem. 29:562, 1957.

Single crystals and particles of colloidal size can be easily carbon-mounted and carbon-replicated. Undissolved, such preparations of particle dispersions preserve the morphology of a complete distribution held rigidly within relatively strong, structureless mounting medium. Selective etching allows identification of the components of mixtures regardless of recognizable geometry. Carbon replicas of single crystals present improved opportunities for obtaining determinative crystallographic data in addition to mere morphology by electron microscopy of a wide selection of substances. Complicated microstructures can be carbon-mounted, and by a process of partial etching and stereoscopy, much can be deduced concerning them. In interpreting the microstructures consideration must be given to the manner in which the carbon deposits and to the effect that particle orientation has upon the electron image intensities.

*THE RELATION BETWEEN MAGNETIC PROPERTIES AND CRYSTAL MORPHOLOGY OF SUBMICRON IRON PARTICLES. J. H. L. WATSON AND M. W. FREEMAN. Am. Inst. Elect. Eng. Special Publication T-91, Proceedings of the Conference on Magnetism and Magnetic Materials, 1956.

The magnetic properties of single, monolithic needles and rods of alpha iron are reported. The crystal structure of the rods and of dendrites is discussed and described from electron microscopic and x-ray diffraction studies and a semi-quantitative description given of how the magnetic properties of alpha iron single crystals can be predicted from their size and shape. Two particular conclusions are emphasized, (1) that all of the types of colloidal crystals described are gentically homologous and (2) that selectivity in the morphology of the crystals, their geometry and anisotropy are directly related to the coercive force.

*Edsel B. Ford Institute for Medical Research.

Abstracts

*SUBMICRON METAL POWDERS. J. H. L. WATSON AND M. W. FREEMAN. Product Eng. p. 182, 1957.

Strength and density of parts made by powder metallurgy depend largely on the diffusion process. With complete diffusion, a sintered compact would be as free of voids and strong as a solidified melt. It is the relation between volume, surface area and intimancy of contact that influences the extent of diffusion.

With metal powders of the size commonly used, the highest practical compacting pressure and sintering temperatures still leave a large proportion of voids where diffusion has not taken place. But by reducing the size of the particle — particularly when these particles are single, integral crystals — the same conditions produce more complete diffusion and a sintered compact of greater strength and density.

One of the most significant things about these submicron powders is that they have such strong interparticle bond and can be made so fine that sintered compacts have strength and density comparable to solid metal. Particles are as fine as in tobacco smoke — some only 50 atoms across; it would take a billion of them to equal the volume of typical metal-powder particle. In addition, with these submicron particles, diffusion or chemical union can take place between metal and organic materials.

*From Edsel B. Ford Institute for Medical Research.